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Efficacy of docetaxel-based chemotherapy following ketoconazole in metastatic castration-resistant prostate cancer: Implications for prior therapy in clinical trials

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Abstract

Objectives: Abiraterone acetate (AA) is a CYP17 inhibitor of androgen synthesis approved for use following docetaxel for metastatic castration-resistant prostate cancer (mCRPC); evaluation in the pre-docetaxel setting is ongoing. Given that the reported efficacy of AA is lower following docetaxel vs. pre-docetaxel, the potential exists for cross resistance given docetaxel's partly androgen receptor targeting activity. The efficacy of docetaxel following ketoconazole (KC), a weaker and nonspecific inhibitor of CYP17, may provide some insights into this potential interaction. We retrospectively evaluated the efficacy of every 3-week docetaxel with prednisone (DP) in mCRPC previously exposed to KC compared to KC-naive patients.

Materials and methods: A randomized phase II trial of men with mCRPC treated with DP + AT-101 (bcl-2 inhibitor) vs. DP plus placebo was analyzed. Both arms were combined for analysis as no significant differences were seen. Overall survival (OS), progression-free survival (PFS), objective response (ORR), pain, and prostate-specific antigen (PSA) response rates were estimated with and without prior KC. Cox proportional hazards regression models were used to estimate the effect of covariates on OS.

Results: Of 220 evaluable men, 40 (18.2%) received prior KC. The median OS with DP-based therapy of KC-naive patients (18.3 months, 95% CI: 15.0, 24.5) and post-KC patients (17.0 months, 95% CI: 9.9, 20.4) was not statistically different ($P = 0.20$). After controlling for prognostic classifications, analyses demonstrated consistent trends for worsening of OS after KC, with (hazard ratios (HRs) 1.33–1.46. Similar unfavorable trends were observed for ORR, PSA declines, and PFS.

Conclusions: In this hypothesis-generating analysis, patients treated with docetaxel-based chemotherapy following prior KC had numerically and consistently worse outcomes than patients not exposed to prior KC. Although the estimated differences did not attain statistical significance, evaluation of outcomes with docetaxel in particular, and all classes of novel and emerging agents following AA, is of clinical importance, given its more potent androgen synthesis inhibition compared with KC. Drug development should take into account the potential impact of previous therapy.

Keywords: Docetaxel; Ketoconazole; Metastatic; Castration resistant prostate cancer

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1. Introduction

Therapy for mCRPC has recently undergone dramatic advances with the addition of multiple classes of novel agents to the therapeutic armamentarium [1–6]. Given such advances, the proper sequencing of these agents becomes of paramount importance, and clinical and biological markers of predicted sensitivity are needed. AA, a CYP17 inhibitor, potently suppresses androgen synthesis and was demonstrated to extend survival in the post-docetaxel setting, where it is currently approved [1]. However, the activity of AA in the pre-docetaxel castration-resistant prostate cancer (CRPC) setting appears to be greater, based on reported rates of PSA decline and PFS in phase 1–2 trials, suggesting possible cross-resistance with docetaxel [7,8]. A phase III trial of AA in the chemonaive pre-docetaxel setting has been completed and results are pending at this time.

Docetaxel, the conventional first-line chemotherapy, is a microtubule stabilizing taxane that has resulted in improvements in survival and palliation of men with metastatic CRPC. A recently postulated and intriguing mechanism of action of docetaxel is the prevention of androgen receptor (AR) trafficking to the nucleus mediated through microtubular disruption, thus suggesting a specific target relevant to CRPC [9,10]. If this AR disruption is an important component of docetaxel sensitivity, this suggests potential cross-resistance with other AR targeting drugs. While incompletely understood, postulated mechanisms of resistance to AA include up-regulation of intratumoral androgen synthesis, AR mutations and AR splice variants, and up-regulation of CYP17 [11,12]. Androgen deprivation may also up-regulate other non-AR-dependent signaling pathways (e.g., PI3K/Akt signaling [10,13]). Hence, exposure to AA could potentially promote resistance to subsequent docetaxel through a number of these redundant mechanisms.

Ketoconazole (KC) is a CYP17 and androgen synthesis inhibitor that has been used for decades to control disease progression in men with CRPC; combination therapy with high dose KC and hydrocortisone (HC) has been demonstrated to have antitumor activity, although extension of survival has not been demonstrated in a randomized trial [14]. Although KC is a less specific and less potent inhibitor of CYP17-mediated androgen synthesis, we hypothesized that examining outcomes with subsequent docetaxel-based therapy in patients with mCRPC exposed or not exposed to prior KC may yield insights into molecular and clinical cross-resistance patterns with CYP17 inhibitors, such as AA and docetaxel. Hence, we conducted a retrospective analysis to determine any differential effect of prior KC in a prospective phase II trial, CS-205, which evaluated docetaxel-prednisone very 3 weeks (DP) combined with either placebo or AT-101 (oral Bcl-2 family inhibitor) [15].

2. Materials and methods

2.1. Patient population

The CS-205 phase II trial was approved by local institutional review boards (IRBs) and conducted at 41 centers in the Russian Federation and the U.S.A. [15]. The stratification factors were pain and Eastern Cooperative Oncology Group (ECOG) performance status (0–1 vs. 2). One patient did not receive any treatment because of disease progression and was excluded from all analyses. The remaining 220 men received a maximum of 17 cycles of DP treatment, unless unacceptable toxicity, progression by PCWG-2 criteria (symptomatic, response evaluation criteria in solid tumors (RECIST), bone scan but not PSA progression alone), or death occurred [15]. AT-101 was not continued after discontinuation of DP. Imaging was obtained every 3 cycles or at symptomatic progression. Men in both arms of the CS-205 trial were combined for analysis, as no significant differences in outcomes were observed.

2.2. Statistical analysis

OS was calculated from randomization date using the Kaplan-Meier method. The primary statistical analysis was the univariate Cox regression exploring whether exposure to prior KC was associated with a difference in OS by log-rank test. Cox proportional hazards regression models were used to estimate the effect of covariates on OS and test for interactions. Secondary analyses were performed based on duration of and response to prior KC to demonstrate the robustness of this potential association using supportive analyses. Secondary outcomes and baseline characteristics were compared between men with and without prior ketoconazole using Fisher's exact tests (binary outcomes), χ^2 tests (categorical), or Wilcoxon rank-sum test (ordinal). All tests were 2-sided and a $P \leq 0.05$ was considered statistically significant with no multiple comparison adjustment performed.

3. Results

3.1. Patient characteristics

The primary results of the CS-205 trial have been reported elsewhere [15]. Briefly, the treatment arms were balanced and outcomes were similar, with median OS of 18.1 vs. 17.8 months [hazard ratio (HR) 1.07, 95% confidence interval (CI) 0.72–1.55, $P = 0.63$] for AT-101-DP and placebo-DP arms, respectively. Secondary endpoints were also similar. Of 220 evaluable men, 40 (18.2%) received prior KC (median duration 2.0 months, maximum 31.1 months) and 6 (15%) had a partial response to KC (Table 1). These 40 men had less visceral disease (15% vs. 28%), more prior radiotherapy (70% vs. 51%), and in-

Table 1
Baseline characteristics of patients

Characteristic	No prior ketoconazole	Prior ketoconazole	*P* value
N	180	40	
Months on ketoconazole			
Median (range)	—	2.0 (0.5–31.1)	
Best response on ketoconazole			
Partial response	—	6 (15.0)	
Stable disease		2 (5.0)	
Progressive disease		23 (57.5)	
Unknown/NA		9 (22.5)	
Age			
Mean (SD)	69.2 (8.5)	69.6 (8.1)	0.90
Liver metastases			
N (%)	12 (6.7)	2 (5.0)	1.00
Visceral disease			
N (%)	50 (27.8)	6 (15.0)	0.11
≥2 Metastatic sites			
N (%)	56 (31.1)	9 (22.5)	0.34
Significant baseline pain			
N (%)	63/175 (36.0)	11/39 (28.2)	0.46
ECOG status			
0	66 (36.7)	13 (32.5)	0.72*
1	103 (57.2)	26 (65.0)	
2	11 (6.1)	1 (2.5)	
Prior surgery			
N (%)	115 (63.9)	24 (60.0)	0.72
Prior radiotherapy			
N (%)	91 (50.6)	28 (70.0)	0.035
PSA progression			
N (%)	149 (82.8)	33 (82.5)	1.00
RECIST progression			
N (%)	37 (20.6)	15 (37.5)	0.038
Bone scan progression			
N (%)	73 (40.6)	22 (55.0)	0.11
Disease stage			
1–2	42/176 (23.9)	14 (35.0)	0.16†
3–4	134 (76.1)	26 (65.0)	
Gleason score at diagnosis			
≤7	61 (33.9)	22 (55.0)	0.49‡
8–10	79 (43.9)	15 (37.5)	
Unknown	40 (22.2)	3 (7.5)	
PSA (ng/ml)			
Mean (SD)	412.1 (1133.9)	169.6 (212.8)	0.38
Median (range)	92.0 (0.6–13,056)	72.1 (3.9–881.3)	
Alkaline phosphatase (u/L)			
Mean (SD)	249.0 (346.8)	218.7 (217.3)	0.62
Median (range)	124 (44–2933)	110 (45–779)	
Baseline hemoglobin (g/dL)			
Mean (SD)	12.5 (1.7)	12.7 (1.6)	0.60
Median (range)	12.6 (8.2–17.0)	12.7 (9.2–16.2)	
Baseline albumin (g/L)			
Mean (SD)	4.3 (0.7)	4.1 (0.6)	0.19
Median (range)	4.4 (2.5–5.7)	4.1 (2.7–5.1)	
PSA doubling time			
N (%) <55 d	100 (55.6)	22 (55.0)	1.00
Risk groups			
Good risk	73 (42.2)	20 (51.3)	0.22
Moderate risk	70 (40.5)	12 (30.8)	
Poor risk	30 (17.3)	7 (18.0)	
PCWG-2 clinical subtypes			
Visceral disease	50 (27.8)	6 (15.0)	0.50
Bone ± nodal disease	118 (65.6)	30 (75.0)	
Nodal disease only	12 (6.7)	4 (10.0)	
Treatment arm			
AT-101	91 (50.6)	19 (47.5)	0.86

RECIST = response evaluation criteria in solid tumors; ECOG = Eastern Cooperative Oncology Group; PSA = prostate specific antigen; PCWG-2 = Prostate Cancer Working Group-2.

* ECOG 1 or 2 vs. 0.

† Stage 3–4 vs. 1–2.

‡ Gleason 8–10 vs. ≤7.

Table 2
Outcomes with docetaxel-based therapy with or without prior ketoconazole

Characteristic	No prior ketoconazole	Prior ketoconazole	*P* value
N	180	40	
Overall survival			
Median (95% CI)	18.3 (15.0, 24.5)	17.0 (9.9, 20.4)	0.20*
6 Months (95% CI)	93.5 (88.6, 96.4)	82.2 (66.3, 91.1)	
1 Year (95% CI)	75.4 (68.0, 81.3)	66.8 (49.8, 79.2)	
Progression-free survival			
Median (95% CI)	10.8 (8.6, 12.2)	9.9 (6.4, 15.4)	0.64*
6 Months (95% CI)	73.9 (66.5, 79.9)	71.4 (54.3, 83.1)	
1 Year (95% CI)	42.9 (34.8, 50.7)	38.7 (23.3, 53.9)	
Response rate (RECIST)			
PR	24 (26.7)	3 (18.8)	0.76†
SD	49 (54.4)	12 (75.0)	
PD	8 (8.9)	1 (6.3)	
NA/other	9 (10.0)	0 (0.0)	
Pain response			
1-Point	65/108 (60.2)	10/18 (55.6)	0.80
2-Point	19/63 (30.2)	2/11 (18.2)	0.72
PSA response			
≥30% Confirmed	107 (59.4)	24 (60.0)	1.00
≥50% Confirmed	92 (51.1)	17 (42.5)	0.38
≥30% Unconfirmed	135 (75.0)	25 (62.5)	0.12
≥50% Unconfirmed	108 (60.0)	20 (50.0)	0.29
PSA decline (%)			
Median by week 12	−45.7%	−28.6%	0.22
Median at any time	−67.0%	−50.1%	0.14

RECIST = response evaluation criteria in solid tumors; CI = confidence interval; PR = partial response; SD = stable disease; PD = progressive disease; NA = not applicable.
* Log-rank test *P* value.
† Comparison of PR vs. other.

creased prior radiological (38% vs. 21%) or bone scan progression (55% vs. 41%) (Table 1).

3.2. Outcomes with docetaxel with or without prior ketoconazole

Efficacy outcomes were not statistically different between KC-naive and post-KC patients receiving DP (Table 2). Median OS of post-KC patients (17.0 months, 95% CI: 9.9, 20.4) was not significantly worse than KC-naive patients (18.3 months, 95% CI: 15.0, 24.5, $P = 0.20$) (Fig. 1). Secondary outcomes in the KC-naive and post-KC patients, including median PFS (10.8 vs. 9.9 months, Supplementary Fig. 1), PSA response rate (51.1% vs. 42.5%), and objective measurable disease response rates (26.7 vs. 18.8%) were also not statistically different (Table 2). However, despite not being statistically significant, patients who had received prior KC performed numerically slightly worse for most outcomes measured than patients who did not receive prior KC (Table 2).

A significant interaction effect between prior KC and treatment group was observed ($P = 0.017$) for OS but not for PFS ($P = 0.084$). In the subgroup of patients who received prior KC, 19 patients received AT-101 whereas 21 received placebo in combination with DP. The median (95% CI) OS was 20.4 [8.8–not reached (NR)] months vs. 15.4 (8.7–17.2) months, and 6-months/1-year OS was 84.2% (58.7–94.6)/73.7% (47.9%–88.1%) and 80.4% (55.8%–92.2%)/60.3% (36.1%–77.8%) for the AT-101 and placebo groups, respectively ($P = 0.029$). The median 6-months and 1-year (with 95% CI) PFS for post-KC patients was 16.4 (4.9–19.6) months, 77.0% (49.7%–90.7%) and 53.3% (28.0%–73.3%) for DP-AT-101 and 9.3 (5.9–11.0) months, 66.7% (42.5%–82.5%) and 28.6% (11.7%–48.2%) for DP-placebo (*P* value = 0.026).

3.3. Outcomes with docetaxel based on duration of and response to prior ketoconazole

Outcomes were examined based on prior exposure to KC <2 or ≥2 months (Supplementary Table 1). Both survival and PFS were not statistically different ($P = 0.45$ and 0.29, respectively) based on duration of prior KC. However, a separation in the curves for survival (Fig. 2) and PFS (Supplementary Fig. 2) were observed in favor of the <2-month duration of prior KC group. No statistical differences were observed with docetaxel-based therapy stratified by prior best response to KC (Supplementary Table 2).

3.4. Outcomes with docetaxel after controlling for prognostic factors

Prior KC demonstrated a trend for worse OS with DP-based therapy after adjusting for baseline stratum and treatment group (HR 1.34, 95%CI: 0.86, 2.09, $P = 0.20$) and adjusting for a nomogram derived from the TAX-327 trial

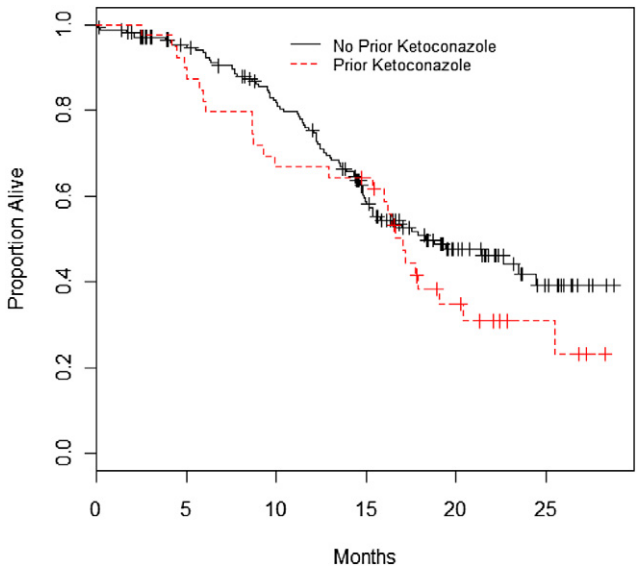

Fig. 1. Overall Survival with docetaxel-based therapy with or without prior ketoconazole. (Color version of figure is available online.)

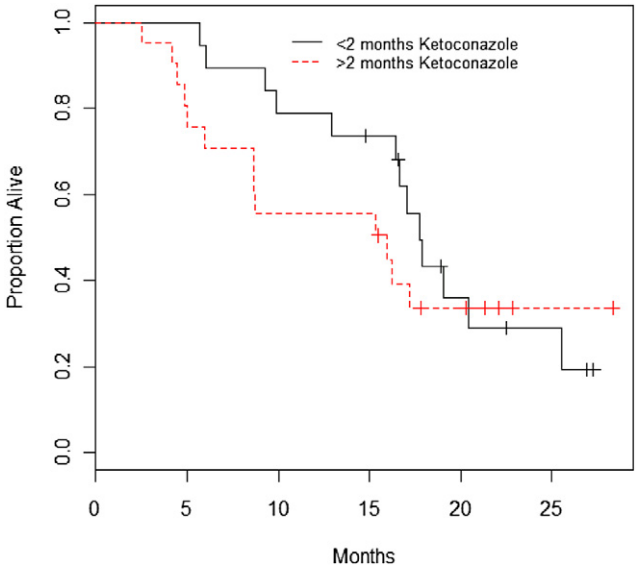

Fig. 2. Overall survival with docetaxel-based therapy by duration of ketoconazole. (Color version of figure is available online.)

(HR 1.33, 95% CI: 0.84, 2.08, $P = 0.22$) (Table 3) [16]. A trend for worse OS was also observed when adjusting for Prostate Cancer Working Group (PCWG)-2 clinical subtypes (HR 1.45, 0.92, 2.29, $P = 0.11$) and baseline PSA (HR 1.46, 95% CI: 0.94, 2.29, $P = 0.095$) [17].

4. Discussion

In this retrospective analysis of a large prospective randomized phase II trial of 220 evaluable men receiving first-line docetaxel-based chemotherapy for mCRPC, we found no evidence for strong differential outcomes based on prior KC exposure. The primary efficacy endpoint, OS, and other secondary endpoints were not statistically different with ($n = 40$) and without prior KC ($n = 180$). However, Cox regression analyses after controlling for stratification factors, nomogram risk estimators, PCWG-2 clinical subtypes, and baseline PSA demonstrated trends for worsening of survival after prior KC, with HRs 1.33–1.46 and P values between 0.095 and 0.31 (Table 3). In addition, all other secondary outcomes, including PFS, PSA and radiographic responses, and pain palliation were numerically poorer in men with prior KC exposure. Moreover, the survival curves demonstrated worse outcomes with prior KC duration >2 months compared with <2 months, although the difference was not statistically significant.

Early discontinuation of KC within 2 months for intolerance may be associated with lower potential for the development of resistance mechanisms and explain the more favorable survival in this group with subsequent docetaxel. Taken together, these consistent trends suggest a potential modest detrimental impact of prior KC on subsequent docetaxel-based therapy. Potentially, analysis of a larger database of KC-treated men may have yielded statistically significant differences. These findings are suggestive of possible mechanisms of chemoresistance induced with longer KC exposure. The caveat is, however, that the proportion of patients who discontinued KC due to intolerance and the timing of prior KC are unknown. There was no association between best prior response to KC and subsequent outcomes with docetaxel, and the results did not attain statistical significance. The possibility of a lead time bias and evolution of a larger number of KC-independent mechanisms of resistance with more advanced disease yielding suboptimal outcomes in those patients receiving prior KC needs to be considered. Conversely, patients selected for KC may have more indolent or nonmetastatic disease, which may be more responsive to subsequent therapy.

Prior KC appeared to yield slightly lower response rates with subsequent AA in phase II trials, although cross-resistance between these agents may be anticipated given their overlapping mechanisms of androgen synthesis inhibition [18]. The utilization of KC is likely to decline with time

Table 3
Cox regression analyses for outcomes with docetaxel-based therapy by prior ketoconazole

	OS		PFS	
Characteristic	HR (95% CI)	P value	HR (95% CI)	P value
Univariate analysis	1.34 (0.86, 2.08)	0.20	1.10 (0.74, 1.63)	0.64
Adjusted for:				
TAX-327 nomogram risk estimate	1.33 (0.84, 2.08)	0.22	1.14 (0.77, 1.71)	0.51
Baseline stratum and treatment group	1.34 (0.86, 2.09)	0.20	1.12 (0.75, 1.66)	0.58
'Risk Groups'	1.26 (0.80, 1.98)	0.31	1.04 (0.70, 1.55)	0.84
PCWG-2 subtype classifications	1.45 (0.92, 2.29)	0.11	1.15 (0.77, 1.72)	0.49
Method of determining PD*	1.23 (0.79, 1.93)	0.36	1.13 (0.76, 1.68)	0.55
Prior surgery/radiotherapy	1.28 (0.82, 2.00)	0.28	1.09 (0.73, 1.61)	0.68
Baseline PSA	1.46 (0.94, 2.29)	0.095	1.17 (0.79, 1.73)	0.45
Baseline visceral disease	1.45 (0.92, 2.28)	0.11	1.16 (0.78, 1.72)	0.48

PSA = prostate-specific antigen; PD = progressive disease; PFS = progression-free survival; OS = overall survival; PCWG-2 = Prostate Cancer Working Group-2.

* RECIST, bone scan, or PSA PD.

because of its toxicity profile (i.e., drug interactions, hepatic and gastrointestinal toxicities), lack of demonstrated survival advantage, and the emergence of multiple promising novel agents. Hence, the clinical importance of these results may be more related to their implication regarding novel agents such as AA, which demonstrate more potent androgen synthesis inhibition. It is possible that the increasing and earlier employment of AA and similar agents may yield resistance mechanisms, potentially more potent compared with KC, and consequently poorer outcomes with subsequent docetaxel-based chemotherapy. More broadly, prior AA or similar potent androgen synthesis inhibitors may promote resistance to a wider spectrum of agents beyond docetaxel (e.g., cabazitaxel [3,19]). In addition to the results presented here, indications of possible cross-resistance has been shown with consistently better response rates and duration of response to AA in the prechemotherapy setting than those reported in the post-docetaxel setting [1,7,8].

While up-regulation of redundant survival pathways (e.g., PI3K) may engender resistance to multiple classes of agents, up-regulation of AR with androgen deprivation may provide a rationale for AR antagonists (e.g., MDV-3100, recently reported to improve outcomes following docetaxel) in combination with or following AA [6,13]. Moreover, androgen deprivation may augment T-lymphocyte-mediated antitumor immunity and enhance the efficacy of immunotherapy [20,21]. Thus, potent androgen deprivation may have differential effects, either negative or positive, on the efficacy of subsequent therapy. The phenomenon of more potent systemic therapy yielding poorer outcomes with subsequent therapy has been observed in other malignancies. The PFS with everolimus or axitinib following sunitinib in metastatic renal cell carcinoma appears poor compared with following other agents such as cytokines [22,23]. Despite excellent initial activity of anti-angiogenic therapy with bevacizumab in glioblastoma and other tumor types, such therapy appears to subsequently promote greater invasive properties in preclinical models [24–27].

Preclinical data indicate that the combination of taxane with PI3K inhibition may restore its antitumor activity in phosphatase and tensin homolog (PTEN) null cells [10]. Rational combinations based on a better knowledge of tumor biology and induced tumor resistance mechanisms may provide advances in progressive disease following potent androgen inhibition. The implication may be that the recent reports of failure of multiple docetaxel and biological agent combinations (e.g., bevacizumab, atrasentan, zibotentan, calcitriol, lenalidomide) to improve survival may not translate to the post-AA setting where more potent mechanisms of resistance may render pathways targeted by these biological agents more relevant. Indeed, in an analysis of the 40 post-KC patients, those receiving subsequent AT-101 in combination with DP in the CS-205 trial appeared to exhibit an extension of survival, in contrast to the overall negative results of this trial. While data specific to the post KC or post-AA setting are lacking, preclinical studies have demonstrated that amplification of Bcl-2 confers resistance to androgen depletion in vivo [28]. Hence, chemobiological combinations based on compelling preclinical rationales may warrant continued exploration following prior AA [29,30].

Most phase III trials for mCRPC do not stratify extensively for prior therapy (e.g., trials in the pre-docetaxel space, docetaxel-based combination space, and post-docetaxel space have been typically conducted with stratifications for clinical prognostic factors). However, sipuleucel-T yields delayed benefits in survival and may warrant consideration as a stratification factor [31]. Similarly, if prior AA yields differential outcomes with subsequent therapy, stratification for prior AA can be justified in randomized trials. A meticulous analysis of outcomes with docetaxel and other agents following AA is warranted to investigate this issue. In addition, multiple novel androgen synthesis inhibitors (TAK-700), androgen receptor inhibitors (MDV-3100, ARN-509), immunotherapeutic agents (ipilimumab, prostvac-TRICOM), and novel biological agents targeting invasion (Src, Met, IGF-1R), cell survival (clusterin), and angiogenesis (VEGF, PLGF) are undergoing vigorous evaluation. Hence, a careful evaluation of the impact of preceding agents needs to be analyzed and considered when designing trials, to account for different interactions with mechanisms of resistance and differentials in subsequent outcomes.

5. Conclusions

In this hypothesis-generating analysis, patients treated with docetaxel-based chemotherapy following prior KC had numerically and consistently worse outcomes than patients not exposed to prior KC. However, the estimated differences were small and did not attain statistical significance. Evaluation of outcomes with docetaxel in particular, and all classes of novel and emerging agents following AA, is of clinical importance, given its more potent androgen synthesis inhibition compared with KC. Drug development should take into account the potential impact of previous therapy.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.urolonc.2012.02.008.

References

[1] de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011; 364:1995–2005.

[2] de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: A randomized open-label trial. Lancet 2010;376:1147–54.
[3] Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363: 411–22.
[4] Fizazi K, Carducci M, Smith M, et al. Denosumab vs. zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: A randomized, double-blind study. Lancet 2011;377: 813–22.
[5] Parker C, Heinrich D, O'Sullivan J, et al. Overall survival benefit of radium-223 chloride (Alpharadin) in the treatment of patients with symptomatic bone metastases in castration-resistant prostate cancer (CRPC): a phase III randomized trial (ALSYMPCA) [abstract 1LBA]. Eur J Cancer, 2011;47(Suppl 2):3.
[6] Press release Medivation and Astellas; 3 November 2011.
[7] Danila DC, Morris MJ, de Bono JS, et al. Phase II multicenter study of abiraterone acetate plus prednisone therapy in patients with docetaxel-treated castration-resistant prostate cancer. J Clin Oncol 2010; 28:1496–501.
[8] Attard G, Reid AH, A'Hern R, et al. Selective inhibition of CYP17 with abiraterone acetate is highly active in the treatment of castration-resistant prostate cancer. J Clin Oncol 2009;27:3742–8.
[9] Zhu ML, Horbinski CM, Garzotto M, et al. Tubulin-targeting chemotherapy impairs androgen receptor activity in prostate cancer. Cancer Res 2010;70:7992–8002.
[10] Gan L, Chen S, Wang Y, et al. Inhibition of the androgen receptor as a novel mechanism of taxol chemotherapy in prostate cancer. Cancer Res 2009;69:8386–94.
[11] Mostaghel EA, Marck BT, Plymate SR, et al. Resistance to CYP17A1 inhibition with abiraterone in castration-resistant prostate cancer: Induction of steroidogenesis and androgen receptor splice variants. Clin Cancer Res 2011;17:5913–25.
[12] Cai C, Chen S, Ng P, et al. Intratumoral de novo steroid synthesis activates androgen receptor in castration-resistant prostate cancer and is up-regulated by treatment with CYP17A1 inhibitors. Cancer Res 2011;71:6503–13.
[13] Murillo H, Huang H, Schmidt LJ, et al. Role of PI3K signaling in survival and progression of LNCaP prostate cancer cells to the androgen refractory state. Endocrinology 2001;142:4795–805.
[14] Small EJ, Halabi S, Dawson NA, et al. Antiandrogen withdrawal alone or in combination with ketoconazole in androgen-independent prostate cancer patients: A phase III trial (CALGB 9583). J Clin Oncol 2004;22:1025–33.
[15] Sonpavde G, Matveev V, Burke JM, et al. Randomized phase II trial of docetaxel plus prednisone in combination with placebo or AT-101, an oral small molecule Bcl-2 family antagonist, as first-line therapy for metastatic castration-resistant prostate cancer. Ann Oncol, 2011 Nov 29 [Epub ahead of print].
[16] Armstrong AJ, Garrett-Mayer ES, Yang YC, et al. A contemporary prognostic nomogram for men with hormone-refractory metastatic prostate cancer: A TAX327 study analysis. Clin Cancer Res 2007; 13:6396–403.
[17] Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: Recommendations of the prostate cancer clinical trials Working Group. J Clin Oncol 2008;26:1148–59.
[18] Ryan CJ, Smith MR, Fong L, et al. Phase I clinical trial of the CYP17 inhibitor abiraterone acetate demonstrating clinical activity in patients with castration-resistant prostate cancer who received prior ketoconazole therapy. J Clin Oncol 2010;28:1481–8.
[19] de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: A randomized open-label trial. Lancet 2010;376:1147–54.
[20] Drake CG, Doody AD, Mihalyo MA, et al. Androgen ablation mitigates tolerance to a prostate/prostate cancer-restricted antigen. Cancer Cell 2005;7:239–49.
[21] Mercader M, Bodner BK, Moser MT, et al. T cell infiltration of the prostate induced by androgen withdrawal in patients with prostate cancer. Proc Natl Acad Sci U S A 2001;98:14565–70.
[22] Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: Final results and analysis of prognostic factors. Cancer 2010;116:4256–65.
[23] Rini Bi EB, Tomczak P, Kaprin A, et al. Axitinib vs. sorafenib as second-line therapy for metastatic renal cell carcinoma (mRCC): Results of phase III AXIS trial. J Clin Oncol 2011;29(Suppl):Abstract 4503.
[24] Keunen O, Johansson M, Oudin A, et al. Anti-VEGF treatment reduces blood supply and increases tumor cell invasion in glioblastoma. Proc Natl Acad Sci U S A 2011;108:3749–54.
[25] Mancuso MR, Davis R, Norberg SM, et al. Rapid vascular regrowth in tumors after reversal of VEGF inhibition. J Clin Invest 2006;116: 2610–21.
[26] Ebos JM, Lee CR, Cruz-Munoz W, et al. Accelerated metastasis after short-term treatment with a potent inhibitor of tumor angiogenesis. Cancer Cell 2009;15:232–9.
[27] Pàez-Ribes M, Allen E, Hudock J, et al. Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis. Cancer Cell 2009;15:220–31.
[28] Raffo AJ, Perlman H, Chen MW, et al. Overexpression of bcl-2 protects prostate cancer cells from apoptosis in vitro and confers resistance to androgen depletion in vivo. Cancer Res 1995;55: 4438–45.
[29] Kelly WK, Halabi S, Carducci MA, et al. A randomized, double-blind, placebo-controlled phase III trial comparing docetaxel, prednisone, and placebo with docetaxel, prednisone, and bevacizumab in men with metastatic castration-resistant prostate cancer (mCRPC): Survival results of CALGB 90401. J Clin Oncol 2010;28:Suppl:18s; Abstr LBA4511.
[30] Scher HI, Jia X, Chi K, et al. Randomized, open-label phase III trial of docetaxel plus high-dose calcitriol vs. docetaxel plus prednisone for patients with castration-resistant prostate cancer. J Clin Oncol 2011;29:2191–8.
[31] Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363: 411–22.