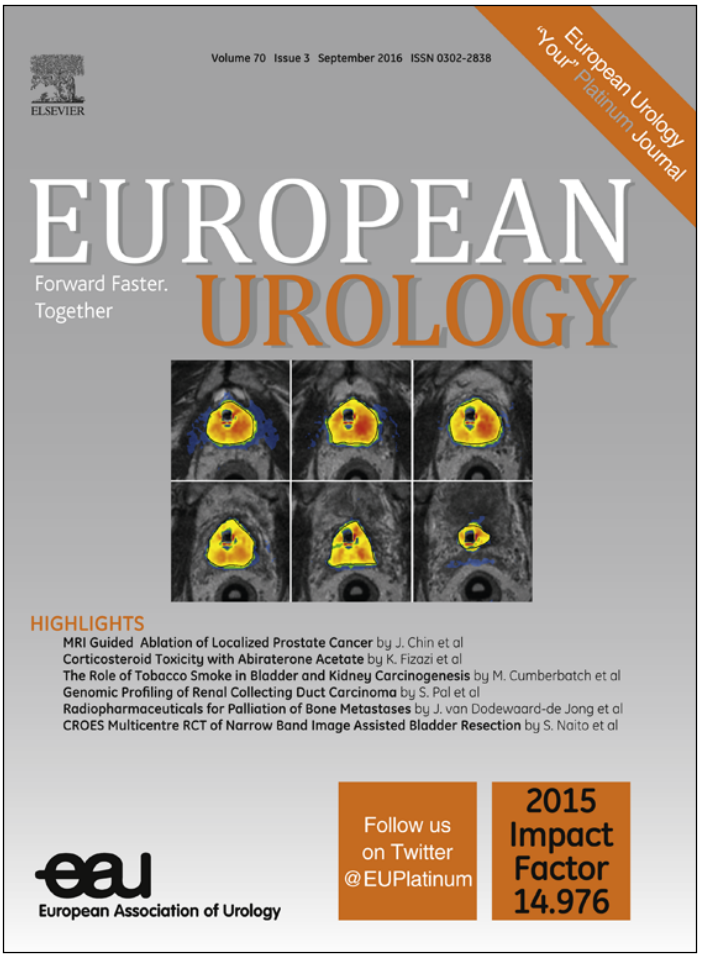

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Brief Correspondence

Docetaxel Activity in the Era of Life-prolonging Hormonal Therapies for Metastatic Castration-resistant Prostate Cancer

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Abstract

For >6 yr, docetaxel with prednisone was the only treatment with survival benefits for metastatic castration-resistant prostate cancer (mCRPC). More recently, in clinical practice, abiraterone acetate has been commonly administered prior to docetaxel for the treatment of mCRPC. Our study aimed to review the activity of docetaxel after prior abiraterone. To this end, we analyzed all retrospective reports in the literature describing the overall survival (OS) of mCRPC patients treated with docetaxel after previous abiraterone. The mean OS observed was 12.7 mo, which suggested a significant decrement compared with the 19.2 mo seen in the updated analysis of the TAX 327 study; however, the data are quite similar to the OS of 13.6 mo (95% confidence interval, 12.1–15.1 mo) described in a retrospective single-institution study of 357 men with mCRPC treated with docetaxel with no prior abiraterone mostly in routine practice (86.3%). Because the characteristics of patients recruited in phase 3 trials tend to differ from the real-world setting, we deemed this data set a relevant comparison. Consequently, despite the limitations of retrospective cross-study comparisons, the data suggest that docetaxel retains activity when used as second-line therapy after abiraterone for mCRPC patients.

Patient summary: We reviewed the activity of docetaxel after prior use of abiraterone and considered the results in the light of the outcomes of docetaxel used as first-line therapy for metastatic castration-resistant prostate cancer (mCRPC) patients in routine practice. We noted that docetaxel retains reasonable activity and is a useful agent for the treatment of mCRPC patients before or after abiraterone.

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For >6 yr, docetaxel with prednisone was the only therapy proven to prolong overall survival (OS) in patients with metastatic castration-resistant prostate cancer (mCRPC) [1] and became the standard of care; however, not all men were considered fit for chemotherapy and thus were not treated with docetaxel. Furthermore, in a retrospective single-institution study of 357 men with mCRPC treated with docetaxel from 2001 to 2011 mostly in routine practice (86.3%), the median OS was 13.6 mo (95% confidence interval [CI], 12.1–15.1 mo) compared with 19.2 mo (95% CI, 17.5–21.3 mo) observed in the updated analysis of the TAX 327 study [2]. The authors concluded that survival of patients with mCRPC treated with docetaxel in clinical practice is shorter and is associated with more toxicity than that of men included in trials [3].

The recent advent of two novel androgen receptor (AR) targeted therapies—abiraterone acetate, a selective irreversible inhibitor of P-450c17, and enzalutamide, a potent

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AR antagonist and signaling inhibitor—changed the therapeutic landscape of mCRPC. Given their improved survival benefit, lower adverse event profile, oral administration, and consequently greater proportions of patients who are candidates for these therapies, they became the more common first-line treatment. Analyses of prescriptions showed that in 2010, 91% of US men with mCRPC fit for available therapy received docetaxel as first-line treatment, whereas in 2013, this number had decreased to only 15%, as 67% of patients were treated with abiraterone as first-line mCRPC therapy [4].

At this juncture, it was questioned whether the efficacy of docetaxel was affected by prior abiraterone. To this end, several retrospective reports identified by a literature search (Appendix) investigated the clinical outcomes of mCRPC patients treated with docetaxel after previous abiraterone [5–9]. In aggregate, results showed that prostate-specific antigen (PSA) decline ≥50% ranged from 13% to 48%, and OS ranged from 12.4 to 14.4 mo (Table 1). Interestingly, some of these papers noted no response to docetaxel in patients who showed primary resistance to abiraterone [6,7]. This led to speculation about the possibility of cross-resistance between abiraterone and docetaxel. Conversely, a report by Schweizer et al, who compared the efficacy of docetaxel in patients who did ($n = 24$) or did not ($n = 95$) receive prior abiraterone, described responses to docetaxel in the group of patients who had no response to prior abiraterone [7]. These results were also supported by a Canadian multicenter retrospective study that retrospectively analyzed 86 patients treated with docetaxel after failure of abiraterone. A PSA decline of ≥50% was observed in 30 of 86 patients (35%; 95% CI, 26–45%), and the median OS was 11.66 mo (95% CI, 9.45–13.88 mo); however, no statistically significant differences in PSA response or OS were observed for patients with no PSA decline, with <50% decline, and with ≥50% decline on abiraterone [9].

The conflicting findings of these retrospective reports highlight the need for prospective multicenter evaluations of therapies rather than drawing conclusions from single-institution reports based on end points of unclear significance such as PSA decline. In this respect, a post hoc analysis of COU-AA-302 revealed that 27% of 100 patients who had docetaxel after abiraterone and at least one PSA measurement on therapy had a confirmed decline of ≥50% [10]. Nonetheless, there was consistency of the median OS for all of these studies of men treated with docetaxel after abiraterone, and the mean OS value was 12.7 mo. At first look, these data would suggest a significant decrement of activity of docetaxel used after abiraterone compared with docetaxel used with no prior abiraterone, as reported in the final survival analysis of TAX 327 (OS was 19.2 mo) [2]. However, if compared with the OS achieved with first-line docetaxel in routine practice [3], the OS of docetaxel after abiraterone reported in similar institutional retrospective reviews appears similar (13.6 vs 12.7 mo). The discrepancy between the results from clinical practice and the OS from the phase 3 clinical trial setting is probably due to the restrictiveness of the eligibility criteria. At baseline, patients in TAX 327 had better prognostic features than those in the series by Templeton et al. [3] (Table 1): poor performance score, 13% versus 29%; Gleason score 8–10, 31% versus 58%; and median PSA, 114 versus 164 ng/ml. As such, it should be noted that the characteristics of the trial population would portend a better prognosis than in the

Table 1 – Patient characteristics and results

Variable	TAX 327 [2]	SWOG 9916 [1]	Templeton et al. [3]	Mezynski et al. [5]	Azad et al. [8]	Aggarwal et al. [9]	Ueda et al. [6]
Type of study	Phase 3 trial	Phase 3 trial	Hospital registry	Hospital registry	Hospital registry	Hospital registry	Hospital registry
After abiraterone	No	No	No	Yes	Yes	Yes	Yes
Patients, *n*	335	386	314	35	86	23	15
Age, yr, median	68	70	71	71	71	67	71
Gleason score, *n* (%)							
≤6–7	141 (42)	–	105 (43)	14 (40)	27 (31)	6 (26)	3 (20)
8–10	104 (31)	–	142 (58)	18 (51)	46 (53)	17 (74)	11 (73)
PS, %							
Poor	13 *	10 ~	29 #	9 #	34 #	–	7 #
Median PSA, ng/mL	114	84	164	232	184	260	67
Sites of disease, *n* (%)							
Bone	301 (90)	324 (84)	273 (87)	33 (94)	81 (94)	21 (91)	12 (80)
Lymph nodes	–	93 (24)	159 (51)	10 (31)	46 (53)	–	6 (40)
Visceral	74 (22)	69 (18)	60 (19)	4 (11)	17 (20)	2 (9)	3 (8)
OS, mo							
Median	19.2	17.5	13.6	12.5	11.66	12.4	14.4
95% CI	17.5–21.3	–	12.1–15.1	10.6–19.4	9.4–13.9	8.2–19.6	6.3–22.4
PSA decline ≥50%, %							
Rate	45	50	45	26	35	48	13
95% CI	40–51	–	39–51	13–43	26–45	–	–

CI = confidence interval; OS = overall survival; PS = performance status; PSA = prostate-specific antigen.
* Karnofsky PS ≤70.
~ SWOG PS ≥2.
# Eastern Cooperative Oncology Group PS ≥2.

real-world setting when one considers the components of prognostic nomograms [11]. This holds particularly true for prostate cancer patients who are often elderly, have comorbidities, and may be more vulnerable to the adverse events of any given therapy, particularly a cytotoxic one such as docetaxel. Consequently, even though in phase 3 trials the OS benefit provides evidence of the clinical activity of docetaxel, we cannot assume the general population will have the same survival rates. The more appropriate comparison might be the aggregate OS data gathered from the studies on docetaxel as second-line therapy after abiraterone beyond a clinical trial setting (12.7 mo) versus the 13.6 mo reported by Templeton et al. [3]. When considered in this light, it would appear that docetaxel after abiraterone maintains a degree of activity similar to that when given without prior abiraterone in routine practice. Unfortunately, the only comparisons that can be made are cross-study comparisons of PSA decline, time to progression, and OS rates from registry data, as randomized controlled trials are not available. Because docetaxel after abiraterone is used at a later and potentially more aggressive stage, one could postulate that it would be less effective. Alternatively, it is known that non–AR-dependent disease is sensitive to docetaxel in CRPC as well as in lung, breast, and gastric cancer.

In conclusion, given the limitations of retrospective cross-study comparisons, the totality of the data would suggest that docetaxel used as second-line therapy after abiraterone retains reasonable activity and is a useful agent for the treatment of mCRPC patients, before or after abiraterone.

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Study concept and design: Francini, Sweeney.
Acquisition of data: Francini.
Analysis and interpretation of data: Francini, Sweeney.
Drafting of the manuscript: Francini.
Critical revision of the manuscript for important intellectual content: Sweeney.
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Appendix A. Appendix–Search terms

The PubMed/Medline, Embase, LILACS, Cochrane Library, and American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) abstracts databases were searched for relevant articles using the following terms: *docetaxel after abiraterone, abiraterone followed by docetaxel, docetaxel with prior abiraterone, abiraterone before docetaxel, abiraterone and subsequent docetaxel.*

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