ORIGINAL ARTICLE
The influence of prednisone on the efficacy of docetaxel in men with metastatic castration-resistant prostate cancer

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INTRODUCTION
Prednisone and other corticosteroids are used frequently in the treatment of advanced prostate cancer. Corticosteroids are sometimes prescribed to alleviate pain from bone metastases,1 for management of cancer-related fatigue2 or to potentially reduce chemotherapy-related toxicity.3 Beyond these palliative uses, corticosteroids have also been associated with favorable antitumor responses.4 In addition, a number of randomized trials in advanced prostate cancer have used corticosteroids (namely prednisone) as the backbone or the control arm of these studies. This includes the study of Tannock et al.5 comparing mitoxantrone plus prednisone vs prednisone alone, which led to Food and Drug Administration approval of the combination for palliation of symptomatic castration-resistant prostate cancer (CRPC). Thus, data on efficacy of many drugs in prostate cancer is interpreted in the context of concurrent corticosteroid use.

Docetaxel was the first chemotherapy agent shown to prolong survival in men with metastatic CRPC (mCRPC). In the pivotal TAX327 study, 75 mg m$^{-2}$ of docetaxel given intravenously every 3 weeks was compared with mitoxantrone given every 3 weeks. As the control group in this study consisted of mitoxantrone and prednisone, patients on the docetaxel arm also received the same dose of 5 mg of prednisone administered orally twice daily.6 The arm receiving every-3-week docetaxel (plus prednisone) demonstrated superior survival, resulting in Food and Drug Administration approval of docetaxel plus prednisone in 2004 for mCRPC7 and quickly replacing the prior standard-of-care consisting of mitoxantrone plus prednisone. Notably, a non-prednisone-containing regimen of docetaxel plus estramustine was also shown to be superior to mitoxantrone plus prednisone,8 but this regimen has fallen out of favor owing to the significant toxicities of estramustine and the questionable added benefit.9 Since 2004, docetaxel has been a cornerstone of treatment for men with advanced prostate cancer. In modern clinical practice, however, prednisone is not always co-administered with docetaxel, for a number of reasons.10 First, some oncologists have concerns about the sequelae of chronic prednisone use, such as glucose intolerance, osteopenia, fluid retention and peptic ulcers, among other risks.11 Furthermore, there is a theoretical risk of activating the androgen receptor (AR) with prednisone, leading to growth of prostate cancer.12 Patients experiencing progression on antiandrogen therapy occasionally have responses to antiandrogen withdrawal;13 one basis for this observation is changes in AR signaling leading to paradoxical AR agonism with antiandrogens.14 Similarly, other AR mutations may allow activation by glucocorticoids. For example, although the wild-type AR
does not engage glucocorticoids, the T878A and L702H mutations in AR allow glucocorticoid binding to the ligand-binding domain, leading to glucocorticoid-mediated activation of downstream androgen-response elements causing growth of cancer cells.

Although docetaxel is frequently given in combination with prednisone based on the results of the TAX327 study, there is no compelling biological evidence for synergy between glucocorticoids and taxanes. Thus, whether prednisone contributes to the efficacy of docetaxel or is merely a vestige of docetaxel’s approval process remains unclear. Two recently presented studies that tested docetaxel in metastatic castration-sensitive disease employed different strategies regarding prednisone. In STAMPEDE, docetaxel and prednisolone were added to androgen-deprivation therapy (ADT) and compared with ADT alone. Patients receiving up to six cycles of chemotherapy had significantly improved survival (77 vs 67 months, hazard ratio (HR) 0.76 (95% confidence interval (CI) 0.63–0.91)). In CHAARTED, patients who received up to 6 cycles of docetaxel plus ADT—without prednisone—also demonstrated significantly improved survival compared with patients receiving ADT alone (57.6 vs 44.0 months, HR = 0.61 (95% CI 0.47–0.80)). The efficacy of both CHAARTED and STAMPEDE protocols casts some doubt to prednisone’s added value in this setting.

This begs the question of whether prednisone is required for patients receiving docetaxel for mCRPC. As there are no prospective trials comparing docetaxel/prednisone with docetaxel alone, we conducted a retrospective analysis to investigate the independent contribution of prednisone on the clinical efficacy of docetaxel. This study was enabled by the fact that not all clinicians using docetaxel to treat prostate cancer at our institution routinely prescribed it with prednisone. We also examined whether prior use of abiraterone (which is also given with prednisone) or ketoconazole (which is given with hydrocortisone) influenced the effect of prednisone on docetaxel. We hypothesized that prednisone would augment the efficacy of docetaxel but only in men who had not received prior corticosteroids in combination with either abiraterone or ketoconazole.

**MATERIALS AND METHODS**

We conducted an institutional review board-approved retrospective study involving consecutive patients treated with first-line docetaxel chemotherapy for mCRPC at our institution between 2004 and 2014. Only patients who received every-3-weekly docetaxel (at a planned dose of 75 mg m⁻²) were included; those receiving weekly docetaxel were not studied. Patients who received additional concurrent therapies (for example, abiraterone, enzalutamide, radium-223), those who had small cell/neuroendocrine histologies and those without follow-up information were excluded.

Patients were divided into two cohorts: those who received docetaxel with concurrent prednisone, and those who received docetaxel alone. These two groups emerged owing to variations in physician practice with respect to routinely prescribing prednisone with docetaxel. We also employed different strategies regarding prednisone. In STAMPEDE, docetaxel and prednisolone were added to androgen-deprivation therapy (ADT) and compared with ADT alone. Patients receiving up to six cycles of chemotherapy had significantly improved survival (77 vs 67 months, hazard ratio (HR) 0.76 (95% confidence interval (CI) 0.63–0.91)). In CHAARTED, patients who received up to 6 cycles of docetaxel plus ADT—without prednisone—also demonstrated significantly improved survival compared with patients receiving ADT alone (57.6 vs 44.0 months, HR = 0.61 (95% CI 0.47–0.80)). The efficacy of both CHAARTED and STAMPEDE protocols casts some doubt to prednisone’s added value in this setting.

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Patients were divided into two cohorts: those who received docetaxel with concurrent prednisone, and those who received docetaxel alone. These two groups emerged owing to variations in physician practice with respect to routinely prescribing prednisone with docetaxel. We also gathered further clinical data on age, year of docetaxel initiation, Gleason score, number and types of prior hormonal therapies received (with particular attention to prior abiraterone or enzalutamide use), presence of visceral metastases, ECOG performance status, presence of pain, baseline hemoglobin, creatinine, alkaline phosphatase and PSA value. The number of cycles of docetaxel administered, date of PSA progression and date of clinical/radiographic progression were recorded. We defined PSA progression as an increase from nadir of 25% (and at least 2 ng ml⁻¹), without requiring a confirmatory PSA measurement. Clinical/radiographic progression was defined as the first of soft tissue progression, bone scan progression or clinical progression. In patients with measureable disease, radiographic progression was determined by applying RECIST (Response Evaluation Criteria In Solid Tumors) criteria (that is, >20% increase in the sum of target lesions). Progression on the basis of bone scan was defined as the development of two new osseous lesions that were not related to a flare phenomenon, similar to Prostate Cancer Working Group 2 criteria, however, confirmatory imaging was not required. Progression on clinical grounds was defined as an escalation of bone pain, a referral for palliative radiation to bone, a referral for surgical stabilization of bone or any other cancer-related complication (for example, obstructive uropathy, myelophthisic bone marrow failure). Data were censored at the time of initiation of further therapy if that date occurred prior to PSA or clinical/radiographic progression.

The primary end point was clinical/radiographic progression-free survival (PFS). We chose PFS as the end point instead of overall survival because most patients received multiple subsequent therapies that may have confounded survival estimates. Secondary end points included >50% PSA response rates and PSA progression-free survival (PSA PFS); PSA response rates correlate with overall survival in meta-analyses of docetaxel-based trials. We also performed subgroup analyses investigating the effect of prednisone on docetaxel’s efficacy in two substrata: men who had previously received abiraterone or ketoconazole, and men who had not received abiraterone or ketoconazole before.

**RESULTS**

We identified 200 consecutive patients for inclusion in the study: 131 men received docetaxel with prednisone, and 69 received docetaxel alone, reflecting different practice patterns at our institution. Summary statistics for each cohort are listed in Table 1. Groups were generally balanced with respect to baseline characteristics. More patients had missing performance status data in the docetaxel-alone group. Prior abiraterone use was significantly more common in the docetaxel/prednisone cohort. Enzalutamide treatment prior to chemotherapy was uncommon in both groups during this time. Notably, all patients who received prior enzalutamide also received abiraterone.

Clinical/radiographic PFS for the entire docetaxel-treated population (depicted in Figure 1) was the primary end point. In an unadjusted analysis, PFS was superior in the docetaxel/prednisone group compared with the docetaxel-alone group (median PFS: 7.8 vs 6.2 months, HR 0.68 (95% CI 0.48–0.97), P = 0.03). The clinical/radiographic PFS advantage for the docetaxel/prednisone cohort was supported by the difference in the number of chemotherapy cycles received. On average, the docetaxel/prednisone cohort received 7.3 cycles of docetaxel compared with 5.7 cycles for the docetaxel-alone cohort. These numbers corresponded to a median of 7 cycles (range 1–19) vs 6 cycles (range 1–13) for docetaxel/prednisone and docetaxel-alone cohorts, respectively.

We next constructed a propensity score-weighted multivariable Cox model to determine factors independently associated with PFS (Table 2). In this model, prednisone use was significantly associated with a reduced risk of clinical/radiographic progression on docetaxel, after adjusting for other factors (HR 0.53 (95% CI 0.35–0.80), P = 0.002). Performance status 0 (vs 1–2) was also associated with reduced risk for clinical/radiographic progression. Gleason score 7 or 8–10 appeared to be more favorable than Gleason score 6, an unexpected finding, although only 6% of patients had Gleason 6 disease. Prior data has shown that the incremental benefit for high-grade tumors is greater with...
Docetaxel compared with lower-grade tumors, but patients with lower-grade tumors have longer survival. Prior abiraterone or ketoconazole use was not significantly associated with inferior PFS in this model; however, the interaction test between treatment with prednisone and prior abiraterone or ketoconazole use was significant.

In a prespecified analysis, we examined clinical/radiographic PFS stratified by prior abiraterone or ketoconazole use (abiraterone is prescribed with 10 mg of prednisone daily and ketoconazole is prescribed with 30 mg of hydrocortisone daily, so patients with prior abiraterone or ketoconazole exposure also had prior corticosteroid exposure). Among corticosteroid-naive patients (that is, no prior abiraterone or ketoconazole), docetaxel/prednisone was superior to docetaxel alone (Figure 2a; median PFS: 8.9 vs 5.9 months, HR 0.49 (95% CI 0.29–0.84), P = 0.009). For abiraterone- or ketoconazole-pretreated patients, a difference in PFS was not seen between docetaxel/prednisone and docetaxel-alone arms (Figure 2b; median PFS: 7.1 vs 6.3 months, HR 0.96 (95% CI 0.59–1.57), P = 0.87).

PSA responses were also analyzed in the two patient cohorts. Best PSA responses are illustrated in the waterfall plots in Figure 3; >50% PSA responses were numerically higher in the docetaxel-alone arm and superior to docetaxel/prednisone use; superior PSA responses in the docetaxel/prednisone group were only observed in those who had not previously received abiraterone or ketoconazole. In a propensity score-weighted multivariable logistic regression model, poor performance status and liver metastases were independently associated with a poor PSA response.

We also compared PSA PFS between cohorts. Median PSA PFS was similar in the docetaxel/prednisone and docetaxel-alone cohorts in an unadjusted analysis (5.5 vs 5.0 months, HR 0.80 (95% CI 0.57–1.13), P = 0.20). For the subgroup of patients without prior abiraterone or ketoconazole use, prednisone use was significantly associated with a reduced risk for PSA progression (HR 0.59 (95% CI 0.36–0.99), P = 0.04). For abiraterone- or ketoconazole-treated patients, however, the differences were non-significant (HR 1.09 (95% CI 0.68–1.75), P = 0.71). In the propensity score-weighted multivariable Cox model, concurrent prednisone use was

### Table 1. Baseline characteristics

| Characteristic                          | All patients (n = 200) | Docetaxel alone (n = 69) | Docetaxel+prednisone (n = 131) | P-value |
|-----------------------------------------|------------------------|--------------------------|-------------------------------|---------|
| Age (years)                             | 68 (45–85)             | 68 (52–85)               | 69 (45–85)                    | 0.45    |
| Performance status                      |                        |                          |                               |         |
| 0                                       | 75 (38%)               | 22 (32%)                 | 53 (40%)                      | 0.001   |
| 1–2                                     | 86 (43%)               | 21 (30%)                 | 50 (50%)                      |         |
| Missing                                 | 39 (20%)               | 26 (38%)                 | 13 (10%)                      |         |
| Hemoglobin (g dl⁻¹)                     | 11.9 (7.7–15.9)        | 11.9 (7.7–15.9)          | 11.9 (8.1–15.3)               | 0.49    |
| Creatinine (mg dl⁻¹)                    | 0.9 (0.5–3.5)          | 1.0 (0.5–3.5)            | 0.9 (0.5–2.1)                 | 0.08    |
| Alkaline phosphatase (IU l⁻¹)           | 137 (39–2109)          | 125 (44–684)             | 149 (39–2109)                 | 0.22    |
| PSA (ng ml⁻¹)                           | 153 (1.2–5327)         | 131.1 (2.9–4861)         | 155.7 (1.2–5327)              | 0.96    |
| Presence of visceral metastasis         |                        |                          |                               |         |
| Liver                                   | 30 (15%)               | 10 (14%)                 | 20 (15%)                      | 0.99    |
| Lung                                    | 24 (12%)               | 6 (9%)                   | 18 (14%)                      | 0.36    |
| Presence of pain                        | 82 (41%)               | 26 (38%)                 | 56 (43%)                      | 0.55    |
| Number of prior hormonal therapies      | 3 (1–5)                | 2 (1–5)                  | 3 (1–5)                       | 0.45    |
| Prior abiraterone–prednisone            | 46 (23%)               | 9 (13%)                  | 37 (28%)                      | 0.02    |
| Prior ketoconazole–hydrocortisone       | 77 (38%)               | 26 (38%)                 | 51 (39%)                      | 0.88    |
| Prior enzalutamide                      | 14 (7%)                | 2 (3%)                   | 12 (9%)                       | 0.15    |

Data reported as median (range) or percentages. P-values for categorical variables are based on Fisher’s Exact test and for continuous variables are based on Wilcoxon–Mann–Whitney test.
associated with a decreased risk of PSA progression (HR 0.53 (95% CI 0.35–0.79), P = 0.002), and the interaction test between prednisone use and prior abiraterone or ketoconazole use was significant (P = 0.04).

**DISCUSSION**

Both prednisone and docetaxel are active agents in the treatment of advanced prostate cancer. In our study, we postulated that docetaxel plus prednisone would be more effective than docetaxel alone. Indeed, patients in the docetaxel/prednisone cohort had superior outcomes (longer PFS, longer PSA PFS, higher PSA response rates) than those receiving docetaxel alone. One possible explanation for this result is that patients received additive benefit from two drugs that are each known to be effective in prostate cancer through different mechanisms.

The activity of prednisone as a single agent has been well characterized. For example, in a randomized phase III trial of mitoxantrone/prednisone vs prednisone alone, patients receiving 10 mg of prednisone daily had > 50% PSA response rates of 24% and a PFS of 4.1 months. Comparable responses were reported in the control arm of the prechemotherapy COU-AA-302 study of abiraterone/prednisone vs prednisone alone. In that study, 24% of patients receiving prednisone 10 mg daily achieved a > 50% PSA response rate, with a PFS of 8.1 months. The mechanism by which prednisone exerts its activity in prostate cancer is at least partially understood. Corticosteroids can suppress adrenal androgens leading to a more complete androgen blockade. They can also inhibit growth of prostate cancer cells through action on various cellular signals, including upregulation of transforming growth factor-beta and downregulation of interleukin-6.

Docetaxel, a taxane chemotherapeutic, acts through its stabilization of microtubules, preventing mitosis. When used for prostate cancer, docetaxel is also believed to interfere with androgen receptor trafficking. Docetaxel’s efficacy has been observed to be reduced when used after multiple hormonal agents, including abiraterone. Because of the proposed cross-resistance between abiraterone and docetaxel, we performed a prespecified subgroup analysis based upon stratification by prior abiraterone or ketoconazole exposure. We believe that these results generate an interesting hypothesis: that prednisone may only enhance the efficacy of docetaxel in those who have not previously received corticosteroids. In current practice, patients are much more likely to have been treated with abiraterone than ketoconazole. Because abiraterone as a single agent was found to cause symptoms of mineralocorticoid excess through its potent effects on adrenal steroid synthesis, abiraterone was subsequently developed to be co-administered with a corticosteroid.

**Table 2.** Propensity score-weighted multivariable Cox model for clinical/radiographic progression-free survival

| Hazard ratio (95% CI) | P-value |
|-----------------------|---------|
| **Treatment**          |         |
| Docetaxel alone        | 1.0 (Ref.) | 0.002 |
| Docetaxel+prednisone   | 0.53 (0.35–0.80) |         |
| **Performance status** |         |
| 0                     | 1.0 (Ref.) | 0.05  |
| 1–2                   | 1.37 (1.003–1.87) |         |
| **Presence of pain**   |         |
| No                    | 1.0 (Ref.) | 0.36  |
| Yes                   | 1.15 (0.86–1.55) |         |
| **PSA**                | 1 (based upon 1 unit change) | 0.91  |
| **Alkaline phosphatase** | 1 | 0.83  |
| **Gleason score**      |         |
| 6                     | 1.0 (Ref.) | 0.05  |
| 7                     | 0.57 (0.33–0.99) | 0.04  |
| 8–10                  | 0.60 (0.36–0.99) | 0.05  |
| **Visceral metastasis: liver** |       |       |
| No                    | 1.0 (Ref.) | 0.36  |
| Yes                   | 1.22 (0.80–1.84) | 0.36  |
| **Visceral metastasis: lung** |       |       |
| No                    | 1.0 (Ref.) | 0.78  |
| Yes                   | 1.07 (0.67–1.69) | 0.78  |
| **Prior Abi/Keto**     |         |
| No                    | 1.0 (Ref.) | 0.18  |
| Yes                   | 0.73 (0.46–1.16) | 0.18  |
| **Interaction**        |         |
| Treatment × prior Abi/ Keto | 1.79 (1.001–3.19) | 0.05  |

Abbreviation: CI, confidence interval.

![Figure 2. Kaplan–Meier plots for clinical/radiographic progression-free survival, showing subsets according to prior use of abiraterone or ketoconazole. (a) No prior use of abiraterone or ketoconazole (hazard ratio 0.49 (0.29–0.84)). (b) Prior use of abiraterone or ketoconazole (hazard ratio 0.96 (0.59–1.57)).](image-url)
Therefore, patients with prior abiraterone exposure in this study would have also had prior chronic prednisone exposure.

Data in the literature about the efficacy of prednisone in various contexts support this hypothesis of reduced prednisone efficacy on subsequent re-challenge. While acknowledging the inherent difficulties of cross-study comparisons, the single-agent activity of prednisone appears reduced when used post-docetaxel. Prednisone was minimally effective, for example, in the control arm of the postchemotherapy COU-AA-301 study of abiraterone/prednisone vs prednisone alone. Patients receiving 10 mg prednisone daily in that study had a >50% PSA response rate of only 6% and a PFS of only 3.6 months. One possible explanation for reduced efficacy of prednisone post-docetaxel is the development of generally more aggressive and refractory disease. Another explanation is that these patients may have developed a glucocorticoid-resistant phenotype through progression on prior prednisone (co-administered with docetaxel).

The characteristics of corticosteroid-sensitive tumors are not well described. The glucocorticoid receptor is observed to be overexpressed in pretreated and advanced prostate cancer. However, steroid responsiveness in the setting of overexpressed or underexpressed glucocorticoid receptor has not been

Figure 3. Waterfall plots depicting best PSA response, according to whether or not prednisone was co-administered with docetaxel. The proportion of men with >50% PSA responses was 48% for those receiving docetaxel alone (a) and was 60% for those receiving docetaxel plus prednisone (P=0.14) (b). Dark bars indicate patients who had received prior abiraterone or ketoconazole; light bars indicate those who had not received prior abiraterone or ketoconazole. Values >100% are truncated (as depicted by the asterisks).

Table 3. Proportion of patients achieving a >50% PSA response, according to prior abiraterone or ketoconazole use

|                                      | All patients (n=200) | Docetaxel alone (n=69) | Docetaxel+prednisone (n=131) | P-value |
|--------------------------------------|----------------------|------------------------|-----------------------------|---------|
| No prior Abi/Keto (n=89)             | 49/89 (55%)          | 14/35 (40%)            | 35/54 (65%)                 | 0.03    |
| Prior Abi/Keto (n=111)               | 62/111 (56%)         | 19/34 (56%)            | 43/77 (56%)                 | >0.99   |

P-values are based on Fisher’s Exact test.
demonstrated. Therefore, a need exists for identification of a biomarker for glucocorticoid responsiveness, similar to ongoing work on biomarkers for AR-directed therapy resistance. Such a marker might allow a clinician to decide whether to administer prednisone together with docetaxel or not.

This study has several important limitations. First, this data represent a single institution’s retrospective experience, and prospective study in a multi-institutional manner would provide the strongest confirmation. Although PFS was the most appropriate end point for this study owing to its time span with different postchemotherapy treatment options available, PFS can be confounded by non-standardized radiographic and clinical assessment schedules. In addition, lactate dehydrogenase is a prognostic factor for patients with prostate cancer, but this was not routinely measured for these patients and thus was unable to be included in our analysis.

In summary, this retrospective analysis suggests that patients who receive docetaxel together with prednisone may have superior outcomes than those receiving docetaxel alone. Although this analysis did not address questions of safety, this putative benefit must be weighed against the potential side effects of prednisone in the individual patient. This study also generates a hypothesis that patients who have received prior prednisone (for example, with abiraterone) may not benefit from additional prednisone administration during docetaxel treatment. Judicious use of prednisone has been suggested based upon preclinical work showing reduced efficacy of enzalutamide in the setting of corticosteroid use, as well as inferior outcomes for concurrent corticosteroid administration in a trial of enzalutamide. Interactions between therapies will become increasingly relevant as the number of drugs available to patients with mCRPC increases further in coming years. In this context, we postulate that prednisone may only be beneficial once during a patient’s treatment course for advanced prostate cancer, and prospective confirmation of this hypothesis is needed.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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