Antitumour activity of docetaxel following treatment with the CYP17A1 inhibitor abiraterone: clinical evidence for cross-resistance?


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Background: Abiraterone and docetaxel are both approved treatments for men with metastatic castration-resistant prostate cancer (mCRPC). Abiraterone pre-docetaxel is currently undergoing evaluation in a phase III study. In vitro studies indicate that taxanes may act by disrupting androgen receptor signalling. We hypothesised that prior abiraterone exposure would adversely impact docetaxel efficacy.

Patients and methods: We retrospectively evaluated activity of docetaxel in mCRPC patients previously treated with abiraterone, using Prostate Cancer Working Group and radiological criteria.

Results: Of the 54 patients treated with abiraterone, 35 subsequently received docetaxel. Docetaxel resulted in a prostate-specific antigen (PSA) decline of ≥50% in nine patients [26%, 95% confidence interval (CI) 13% to 43%], with a median time to PSA progression of 4.6 months (95% CI 4.2% to 5.9%). PSA declines ≥30% were achieved by 13 patients (37%, 95% CI 22% to 55%). The median overall survival was 12.5 months (95% CI 10.6–19.4). All patients who failed to achieve a PSA fall on abiraterone and were deemed abiraterone-refractory were also docetaxel-refractory (N = 8). In the 24 patients with radiologically evaluable disease, partial responses were reported in four patients (11%), none of whom were abiraterone-refractory.

Conclusion: The activity of docetaxel post-abiraterone appears lower than anticipated and no responses to docetaxel were observed in abiraterone-refractory patients.

Key words: abiraterone, androgen receptor, castration-resistant prostate cancer, docetaxel, response rate

introduction

Prostate cancer is the most prevalent cancer in men [1] and the second leading cause of male cancer-related deaths [2]. In TAX327, reported in 2004, the combination of three-weekly docetaxel and prednisone showed a median 2.4-month improvement in overall survival (OS) when compared with mitoxantrone and prednisone in men with metastatic castration-resistant prostate cancer (mCRPC) [3]. Docetaxel is a semi-synthetic taxane that irreversibly binds to β-actin, altering microtubule polymerisation dynamics, impacting cell mitosis and interphase microtubule function and thus triggering apoptosis [4]. Moreover, several recent studies have reported that tubulin-targeting drugs cause cytoplasmic androgen receptor (AR) sequestration ex vivo [5, 6] and in circulating tumour cells [7], significant down-regulation of AR and prostate-specific antigen (PSA) expression and nuclear accumulation of the forkhead transcription factor family member FOXO1, a potent repressor of AR function [8, 9]. Overall, these studies provide strong in vitro evidence that the antitumour activity of docetaxel is at least in part associated with disruption of AR signalling.

Several studies have now confirmed that AR signalling remains a key driver in mCRPC, including the recent clinical studies of abiraterone acetate (abiraterone) [10, 11]. Abiraterone is a potent and selective small-molecule inhibitor of CYP17A1, a key enzyme for androgen and estrogen synthesis. The recently reported phase III trial in men who had previously received docetaxel reported a 4.6-month improvement in OS for patients receiving 10 mg prednisone daily and abiraterone when compared with prednisone alone [12, 13]. Abiraterone is also currently undergoing evaluation in a phase III trial in chemotherapy-naïve patients (ClinicalTrial.gov identifier NCT00887198). Phase II data from multiple
centres suggest that abiraterone may be more active when delivered before chemotherapy, with higher response rates and longer durations of response compared with post-chemotherapy [14–17]. These data suggest that there may be a common mechanism of action and cross-resistance between abiraterone and taxanes. We hypothesized that the antitumour activity and clinical benefit from docetaxel following treatment with abiraterone would be reduced. We therefore retrospectively evaluated the clinical antitumour activity of docetaxel in patients previously treated with abiraterone.

**materials and methods**

**eligibility**

Patients with mCRPC treated in the Royal Marsden NHS Foundation Trust (RM) within the first-in-man continuous dosing phase I/II clinical study (COU-001; previously reported [14]) were identified and their records accessed through the RM computer database. Patients with evidence of disease progression on abiraterone who proceeded to receive docetaxel were selected and their data were analysed. All patients enrolled in the phase I/II disease progression on abiraterone who proceeded to receive docetaxel were accessed through the RM computer database. Patients with evidence of docetaxel in patients previously treated with abiraterone.

**treatment plan and evaluations**

Docetaxel was administered i.v. at the standard dose of 75 mg/m² every 3 weeks as a 1-h infusion with dexamethasone prophylaxis and oral prednisolone 5 mg twice daily as described previously [3]. Docetaxel dose was reduced for toxicity according to standard protocol. A baseline medical history and physical examination were performed on all patients. Blood tests, including PSA, were measured every three weeks, and radiological assessments, including computed tomography scans of the thorax, abdomen and pelvis and bone scans, were carried out every 3 to 6 months. Follow-up data, including time to progression and date of death, were available for all patients.

**outcome measures**

PSA response rates were measured using Prostate Cancer Working Group 2 (PCWG 2) criteria [19, 20]. As recommended by the PCWG 2, PSA response was defined as 50% declines from baseline and a 25% increase confirmed with a second PSA reading a minimum of 3 weeks later was used to determine PSA progression and response duration. In line with PCWG 2 criteria, waterfall plots with maximum PSA change were constructed. RECIST v 1.0 [21] was used to assess soft tissue disease. Progression of bone disease was defined using PCWG 2 criteria, namely a confirmed increase of at least two new lesions on bone scan. Median OS was measured from the start of docetaxel treatment to death or censoring on 2 December 2010. Median time to PSA progression was the time from start of docetaxel therapy until PSA progression as defined by PCWG 2 criteria. Survival and PSA progression were calculated using Kaplan–Meier estimates (using Stata v 10.1, StataCorp LP, Texas, USA). Statistical analysis as defined in the text was used to test the null hypothesis that response to docetaxel in previously abiraterone-refractory patients was 33%, equal to our observed proportion in abiraterone-sensitive patients.

**results**

**patient population**

Between December 2005 and November 2007, 54 chemotherapy-naive patients were treated with abiraterone in our phase I/II clinical trial [14]. To date, four patients continue on abiraterone. Fifteen patients stopped but did not subsequently receive docetaxel: six were good-risk patients (five alive and one dead); four were intermediate risk (all dead) and five were poor risk (four dead and one alive). The remaining 35 patients progressed on abiraterone and subsequently received docetaxel. The characteristics of the latter 35 patients are shown in; Table 1. The majority were either in a good (46%) or intermediate (46%) risk group. The median age before starting docetaxel was 71 years (range: 61–78 years).

**Table 1.** Baseline characteristics of 35 patients treated with docetaxel post-abiraterone

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71</td>
<td>52–85</td>
</tr>
<tr>
<td>Gleason score</td>
<td>6–7</td>
<td>14</td>
</tr>
<tr>
<td>Haemoglobin, normal values 13–17 (g/dl)</td>
<td>11.9</td>
<td>9.6–14.9</td>
</tr>
<tr>
<td>Albumin, normal values 30–50 (g/l)</td>
<td>34</td>
<td>26–42</td>
</tr>
<tr>
<td>LDH, normal values 98–192 (U/L)</td>
<td>190</td>
<td>112–2475</td>
</tr>
<tr>
<td>ALP, normal values 24–110 (U/L)</td>
<td>172</td>
<td>33–7035</td>
</tr>
<tr>
<td>Baseline PSA (μg/l)</td>
<td>232</td>
<td>19–4760</td>
</tr>
<tr>
<td>Prior hormone therapy, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LHRH analogues</td>
<td>35 (100)</td>
<td></td>
</tr>
<tr>
<td>Anti-androgens</td>
<td>35 (100)</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>25 (71)</td>
<td></td>
</tr>
<tr>
<td>Diethylstilboestrol</td>
<td>16 (46)</td>
<td></td>
</tr>
<tr>
<td>ECOG PS</td>
<td>0–1</td>
<td>32 (91)</td>
</tr>
<tr>
<td>N [%]</td>
<td>2</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Sites of metastases, N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone only</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Bone + lymph node</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Bone + lymph node + visceral</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Visceral</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Docetaxel cycles, N</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Median</td>
<td>2–12</td>
<td></td>
</tr>
<tr>
<td>Prognostic factors, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>15 (44)</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>16 (46)</td>
<td></td>
</tr>
<tr>
<td>Visceral metastases</td>
<td>4 (11)</td>
<td></td>
</tr>
<tr>
<td>Bone progression</td>
<td>19 (54)</td>
<td></td>
</tr>
<tr>
<td>Risk groups, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>16 (46)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>16 (46)</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>3 (9)</td>
<td></td>
</tr>
</tbody>
</table>

*Risk groups as per Armstrong et al. [18].

ALP, alkaline phosphatase; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; LHRH, Luteinizing Hormone–Releasing Hormone; PS, performance status; PSA, prostate-specific antigen.
52–85 years) and the majority of patients had bone-only metastases. All patients had received treatment with an anti-androgen and 46% had received diethylstilbestrol. Twenty-five patients (71%) had received single-agent dexamethasone, but no patient received ketoconazole or chemotherapy before starting docetaxel.

Eight patients who did not have a ≥50% fall in PSA on abiraterone were called abiraterone-refractory (Table 2 and Supplemental Table S1, available at *Annals of Oncology* online, group 1). Overall, 27 patients achieved a ≥50% PSA decline with abiraterone (Table 2 and Supplemental Table S1, available at *Annals of Oncology* online, groups 2 and 3). Thirty-four of the 35 patients progressed by PSA while on abiraterone, and one patient had solely evidence of radiological disease progression. Docetaxel was commenced mainly for progressive bone disease on imaging (in 20 patients; 57% of cohort) with worsening of pain in 16 patients (46% of cohort).

docetaxel dose intensity delivered

All patients started on the planned dose of 75 mg/m² docetaxel every 3 weeks. The median number of docetaxel courses administered was six (range: 2–12); the median duration of treatment was 5 months. Six patients (19%) had a dose reduction, five due to grade 3 or 4 neutropenia and one for nausea and vomiting. Six patients (19%) required a dose delay with a median delay of 13 days (range: 7–21 days); two patients due to docetaxel toxicity (one developed grade 3 transaminitis and the other grade 3 fatigue), one patient developed grade 3 hyperglycaemia and a urinary tract infection requiring hospital admission and one patient was delayed after cycle 1 to accommodate radiotherapy treatment for nerve root compression and subsequently received a further cycle of treatment due to declining performance status. Two patients had a treatment delay for unrelated reasons (holiday and routine urinary stent change). Nine patients received at least 10 cycles (one patient received 12), correlating with planned docetaxel treatment delivery in 26% of patients. Docetaxel was discontinued due to poor performance status and/or rising PSA in 22 patients (Supplemental Table S1, available at *Annals of Oncology* online) and due to radiological progression in six patients. Nine of 35 patients progressed by or at 12 weeks, mainly with PSA progression, but including four patients with both PSA and radiological progression. The total dose intensity achieved in our cohort was 79%; for patients who progressed before or at 12 weeks, it was 55%.

### Table 2. Decline in PSA and time on treatment with abiraterone and docetaxel

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>% PSA drop on abiraterone, median (range)</th>
<th>Duration on abiraterone (months), median (range)</th>
<th>% PSA drop on docetaxel, median (range)</th>
<th>Cycles of docetaxel, median (range)</th>
<th>Risk groups:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>9 (0–38)</td>
<td>5 (2–14)</td>
<td>0 (0–49)</td>
<td>3 (2–10)</td>
<td>Good [N];</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>91 (55–99)</td>
<td>24 (7–35)</td>
<td>62 (55–89)</td>
<td>9 (7–12)</td>
<td>Intermediate [N];</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>88 (52–99)</td>
<td>15 (2–29)</td>
<td>8 (0–44)</td>
<td>6 (2–10)</td>
<td>Poor [N];</td>
</tr>
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<td></td>
<td></td>
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</tr>
</tbody>
</table>

Group 1: AA refractory, D refractory; Group 2: AA response, D response; Group 3: AA response, D refractory.

AA, abiraterone acetate; D, docetaxel; PSA, prostate-specific antigen.

Figure 1. Kaplan–Meier plot showing overall survival (A) and time to PSA progression (B). Eleven patients were alive at data closure and were censored for this analysis.

docetaxel antitumour activity post-abiraterone

All of the patients who failed to achieve a ≥50% PSA fall on abiraterone were subsequently docetaxel-refractory (N = 8; Table 2 and Supplemental Table S1, available at *Annals of Oncology* online, group 1), PSA falls by ≥50% were recorded in nine patients (26%, 95% confidence interval (CI) 13% to 43%). A PSA decline of ≥30% was achieved by 13 patients (37%, 95% CI 22% to 55%); 36% of good-risk group, 47% of intermediate-risk group and none of the patients from the poor-risk group. The median time to PSA progression was 4.6 months (95% CI 4.2–5.9) as shown in Figure 1B. Of the 24 patients assessable radiologically, 4 (11%) attained confirmed partial responses (PR), none of whom were abiraterone-refractory. The PR was associated with a decline in ≥50% PSA in three patients. Median OS was 12.5 months (95% CI 10.6–19.4) (Figure 1A). A waterfall plot of maximal PSA change is shown in Figure 2.
There were 13 patients with no PSA decline (37%). Out of 27 patients who had a ≥50% PSA decline with abiraterone, 9 had a ≥50% PSA decline with docetaxel (30%; Table 2 and Supplemental Table S1, available at *Annals of Oncology* online, ‘group 2’) and 18 did not (60%; Table 2 and Supplemental Table S1, available at *Annals of Oncology* online, ‘group 3’) (Supplemental Figure S1, available at *Annals of Oncology* online). The null hypothesis that response to docetaxel in previously abiraterone-refractory patients is 33%, equal to the observed proportion in abiraterone-sensitive patients, may be rejected with borderline significance (two-sided P value = 0.05868, exact binomial test).

**docetaxel tolerability post-abiraterone**

Docetaxel was well tolerated with no unexpected toxicity. The majority of reported side-effects were grade 1 and 2, as defined by Common Terminology Criteria for Adverse Events version 3.0. Grade 3/4 neutropenia was experienced by 14 patients (40%, 95% CI 24% to 58%). One patient developed grade 3 peripheral neuropathy following 10 cycles of docetaxel. Other grade 3 side-effects were vomiting (1), fatigue (1), diarrhoea (1), and depression (1). One patient died 25 days following cycle 2 possibly due a lower respiratory infection with a background of neutropenia.

**discussion**

In this study, we evaluated docetaxel activity, using PSA-based criteria and RECIST, in a consecutive group of 35 patients treated with abiraterone followed by docetaxel. To our knowledge, this is the first report describing response to docetaxel in patients treated with abiraterone. Comparing outcome parameters across different studies can be misleading, but the expected antitumour activity of three-weekly docetaxel and continuous prednisone as documented in the large phase III randomised TAX-327 study is a 45% rate of PSA fall by ≥50%, a 12% radiological response rate by RECIST and a median OS of 18.9 months [3]. To compare first-line treatment response in a similar group of patients to the ones reported in this study, we also evaluated the cohort of patients who received first-line docetaxel at our institution before participating in the COU-003 phase II study of post-chemotherapy abiraterone [17]. This study accrued patients at the same time as the chemotherapy-naïve COU-001 study reported in this manuscript: a ≥50% PSA decline was observed in 13 of 24 patients (54%), which was similar to the TAX327 data. In contrast, we here report a ≥50% PSA decline rate of 26% with docetaxel after abiraterone and a median time to PSA progression of 4.6 months and OS from commencement of docetaxel of only 12.5 months. These data could support the hypothesis that cross-resistance between these agents may exist and support preclinical evidence that the antitumour activity of docetaxel may be related to its impact on AR signalling. Moreover, another explanation for our findings could be high intratumoral androgens in patients discontinuing abiraterone, reducing docetaxel antitumour activity. The possibility that docetaxel acts by suppressing AR expression and therefore interferes with AR function raises the likelihood that AR overexpression or mutation may also contribute to docetaxel resistance. This hypothesis merits further evaluation preclinically.

The activity of abiraterone similarly also appears to differ according to its sequencing with docetaxel. The antitumour activity of abiraterone post-docetaxel was established in the abiraterone phase III study published this year [12]. Of 797 patients receiving abiraterone and prednisone, ≥50% PSA responses were documented in 29% of patients, with an overall response rate by RECIST of 14% and median OS of 14.8 months. Unfortunately, patients were not stratified according to prior response to docetaxel. Previous phase II data in the post-chemotherapy setting showed ≥50% PSA declines in 36%–51% participants [16, 17]. Although data from the phase III trial of pre-chemotherapy abiraterone acetate are awaited, phase II data suggest a markedly higher rate of ≥50% PSA declines. In our institution, we observed ≥50% PSA declines in 28 (67%) of 42 patients and PR by RECIST in 37.5% of the 24 patients with measurable disease [14]. In the other pre-chemotherapy phase II trial, ≥50% PSA declines were observed in 26 of 33 (79%) patients and time to PSA progression was 16.3 months [15]. These data indicate that abiraterone is more active pre-docetaxel and further supports the likelihood of cross-resistance between these agents.

It could be argued that the lower antitumour activity of docetaxel following abiraterone is a function of patients having more advanced disease; this, however, fails to explain the lack of impact of an active drug on the most frequently utilized measures of anticancer activity in this disease including PSA and soft tissue disease. One explanation for the disparate results could be an imbalance in baseline characteristics, but this seems unlikely considering the two cohorts. Although the baseline median PSA was lower in the TAX 327 cohort than in our study (114 compared with 232 ng/ml), visceral disease (which can carry a poorer prognosis) was more prevalent in the TAX 327 cohort (22% compared with 9% in our cohort). Moreover, using risk group stratification as described by Armstrong et al. [18], the majority of patients in this report were in good- or intermediate-risk groups. We observed lower than expected PSA decline rates in each of the risk groups. Our data are limited by the small sample size, the retrospective nature of the study and as this is a single-institution experience. A prospective sequencing trial of abiraterone followed by docetaxel versus docetaxel followed by abiraterone could confirm our observations but would be challenging to perform due to the absence of suitable surrogates of response.

![Figure 2](image_url)
However, if abiraterone becomes available in the pre-
chemotherapy setting, a confirmatory assessment of the
response to sequential agents could be undertaken using
prospectively collected data.

disclosures

Abiraterone acetate was developed at The Institute of Cancer Research, which therefore has a commercial interest in the
development of this agent. All the authors are employees of The
Institute of Cancer Research. GA has received consulting fees
from Janssen-Cilag, Veridex and Millenium Pharmaceuticals;
lecture fees from Janssen-Cilag, Ipsen and Sanofi-Aventis; and
grant support from AstraZeneca, and has served as an
uncompensated advisor to Cougar Biotechnology. GA is listed
on the ICR rewards to inventors of abiraterone scheme. JSdB
has received consulting fees from Ortho Biotech Oncology
Research and Development (a unit of Cougar Biotechnology);
consulting fees and travel support from Amgen, Astellas,
AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb,
Dendreon, Enzon, Exelixis, Genentech, GlaxoSmithKline,
Medivation, Merck, Novartis, Pfizer, Roche, Sanofi-Aventis,
Supergen and Takeda; and grant support from AstraZeneca. CP
has received lecture fees from Sanofi-Aventis. The COU-001
study was sponsored by Cougar Biotechnology, which has now
been acquired by Johnson & Johnson. The remaining authors
have declared no specific conflicts of interest.

references

3. Tannock IF, de Wit R, Berry WR et al. Docetaxel plus prednisone or mitoxantrone
   plus prednisone for advanced prostate cancer. N Engl J Med 2004; 351:
   1502–1512.
   (Taxotere) in xenograft models is not limited to bcl-2 phosphorylation. Invest New
5. Jiang J, Huang H. Targeting the androgen receptor by Taxol in castration-resistant
   impairs androgen receptor activity in prostate cancer. Cancer Res 2010; 70:
   7992–8002.
7. Darshan MS, Loftus MS, Thadani-Mukero M et al. Taxane-induced blockade to
   nuclear accumulation of the androgen receptor predicts clinical responses in
8. 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:
   8386–8394.
   androgen receptor and prostate-specific antigen but not prostate-specific
   membrane antigen in prostate cancer cell lines: implications for PSA surrogacy.
10. Attard G, Cooper CS, De Bono JS. Steroid hormone receptors in prostate cancer:
11. Mohler JL, Gregory CW, Ford OH et al. The androgen axis in recurrent prostate
12. de Bono JS, Logothetis CJ, Molina A et al. Abiraterone and increased survival in
    enumeration as an efficacy response biomarker of overall survival (OS) in
    metastatic castration-resistant prostate cancer (mCRPC): planned final analysis
    (FA) of COU-AA-301, a randomized double-blind, placebo-controlled phase III
    study of abiraterone acetate (AA) plus prednisone (P) post docetaxel. J Clin Oncol
    2011; 29 (Suppl) [Abstr LBA4517].
    acetate is highly active in the treatment of castration-resistant prostate cancer. J
15. Ryan CJ, Shah S, Efstathiou E et al. Phase II study of abiraterone acetate in
    chemotherapy-naive metastatic castration-resistant prostate cancer displaying
    bone flare discordant with serologic response. Clin Cancer Res 2011; 17:
    4854–4861.
16. 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-
17. Reid AH, Attard G, Danila DC et al. Significant and sustained antitumor activity in
    post-docetaxel, castration-resistant prostate cancer with the CYP17 inhibitor
18. Armstrong AJ, Tannock IF, de Wit R et al. The development of risk groups in
    men with metastatic castration-resistant prostate cancer based on risk factors for
    phase II clinical trials in androgen-independent prostate cancer: recommendations
    from the Prostate-Specific Antigen Working Group. J Clin Oncol 1999; 17:
    3461–3467.
20. 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
21. Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the
    response to treatment in solid tumors. European Organization for Research and
    Treatment of Cancer, National Cancer Institute of the United States, National
    Cancer Institute of Canada. J Natl Cancer Inst 2000; 92:
    205–216.