Response to Subsequent Docetaxel in a Patient Cohort With Metastatic Castration-Resistant Prostate Cancer After Abiraterone Acetate Treatment

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Abstract

In this study, clinical outcomes after docetaxel therapy in 23 patients with metastatic castration-resistant prostate cancer (mCRPC) who progressed after treatment with abiraterone acetate (AA) were retrospectively evaluated. Subsequent docetaxel therapy led to ≥ 50% prostate-specific antigen (PSA) decline in 11 patients (48%) of patients; this outcome was not affected by pattern of AA resistance. The PSA response rates suggest that docetaxel and AA are not cross-resistant; however, further prospective study is required.

Introduction/Background: Docetaxel or AA are therapeutic options for mCRPC. We retrospectively analyzed clinical outcomes with subsequent docetaxel in patients with mCRPC after disease progression (DP) with AA to evaluate cross resistance between these therapies. **Patients and Methods:** Patients with chemotherapy-naive mCRPC who were treated with AA in previously reported phase I to III trials, who had DP, and were subsequently treated (not on study) with docetaxel, were included. Acquired AA resistance was defined as: PSA decline > 50% from baseline or radiographically stable disease for ≥ 8 months, with subsequent DP. All other patients were defined as having primary AA resistance. Efficacy outcomes after docetaxel therapy were analyzed. **Results:** We identified 23 patients who were treated with docetaxel after DP with AA, including 14 (61%) with acquired and 9 (39%) with primary AA resistance. Median duration between discontinuation of AA and docetaxel initiation was 2.7 months (range, 0.2-14.7 months). Subsequent docetaxel therapy led to ≥ 30% PSA decline in 15 patients (65%) and ≥ 50% PSA decline in 11 patients (48%). Median OS from date of first docetaxel dose was 12.4 months (95% confidence interval, 8.2-19.6). Patients with previous primary versus acquired AA resistance had similar outcomes with subsequent docetaxel therapy. **Conclusion:** In this retrospective analysis, the type of AA resistance did not appear to affect outcomes with subsequent docetaxel. The PSA response rates observed suggest a lack of cross-resistance between docetaxel and AA, but prospective studies are needed to evaluate for potential cross-resistance and optimize sequences of therapy in patients with mCRPC.

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Introduction

Metastatic castration-resistant prostate cancer (mCRPC) is a lethal form of the disease, and accounts for more than 29,000 deaths annually in the United States.[1] Within the past decade, multiple new therapeutic modalities have produced declines in serum prostate-specific antigen (PSA) and objective tumor responses, lengthened overall survival, and palliated symptoms in patients with mCRPC. Such therapies include taxane-based chemotherapy, radiopharmaceuticals, immunotherapy, androgen synthesis inhibitors such as abiraterone acetate (AA), and potent androgen receptor (AR) antagonists, including enzalutamide.[2-8] In current clinical practice, patients are often treated sequentially with single-agent therapy until the time of disease progression or cumulative toxicity. Several key questions have emerged within the paradigm of sequential therapy for mCRPC: (1) Is there an optimal sequence of therapy?

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(2) Does previous therapy with one therapeutic modality result in cross-resistance to other modalities? (3) Can subcategorizing patients on the basis of previous patterns of treatment resistance have predictive utility to help guide the choice of subsequent treatment?

It is not known whether previous therapy with an androgen synthesis inhibitor results in cross-resistance to therapy with antitubule agents, such as docetaxel. If cross-resistance exists between these modalities of therapy, primary resistance to androgen synthesis inhibitors might be predictive of refractoriness to subsequent treatment with docetaxel. Some retrospective studies have suggested the potential for cross-resistance between androgen synthesis inhibitors, including ketoconazole and AA, and subsequent taxane-based chemotherapy,[9] and others have failed to demonstrate compelling evidence for cross-resistance.[10] In one retrospective study, AA-refractory patients were defined as those without PSA decline > 50% from baseline.[9] In this subgroup of AA-refractory patients, no patients had a decline in PSA with subsequent docetaxel therapy.[9]

Taxane-mediated inhibition of AR nuclear transport and AR-mediated gene transcription might provide the mechanistic link for potential cross-resistance with androgen signaling inhibition.[11,12] It is hypothesized that previous therapy with potent inhibitors of the androgen signaling pathway, including AA, might lead to the emergence of treatment-resistant subclones of cancer cells that are less "androgen responsive" and thus less likely to respond to subsequent docetaxel chemotherapy.

The objective of the current study was to evaluate potential cross-resistance between androgen synthesis inhibitors and taxane-based chemotherapy. In this retrospective analysis of an independent cohort of patients with mCRPC who had disease progression with AA therapy, we examined disease outcomes with subsequent treatment with docetaxel. For this analysis, patients with radiographic stability for at least 8 months or PSA decline $\geq$ 50% from baseline were considered to have acquired resistance, and all others to have primary AA resistance. The cutoff for radiographic disease stability of at least 8 months was chosen because this was the observed approximate median radiographic progression-free survival in the prednisone with placebo control arm in the phase III study of AA in chemotherapy-naive mCRPC.[5]

Methods

Study Population and AA Treatment Schedule

Patients with mCRPC who were treated with AA until the time of disease progression in phase I/II (NCT00473746) and III (NCT00887198) clinical trials and had available data on outcomes with subsequent docetaxel chemotherapy were included in this retrospective, single-institution analysis.

The eligibility criteria for the clinical trials of AA have been reported.[5,13] Patients were chemotherapy-naive and had metastatic prostate cancer with disease progression despite castrate levels of serum testosterone (< 50 ng/dL). In the phase I study, the dose of AA ranged from 250 to 1000 mg/d, with or without concomitant prednisone. In the phase II and III studies, patients received standard dosing (AA 1000 mg/d in modified fasting state concomitantly with prednisone 5 mg orally twice daily). Patients were treated with AA until the time of disease progression according to Prostate Cancer Working Group (PCWG) or PCWG2 criteria,[14,15] unacceptable toxicity, or study withdrawal.

The timing and choice of therapy after AA, and methods of response assessment, were per the discretion of the treating physician. Docetaxel schedules included weekly regimens (35 mg/m^2 weekly; n = 2) or every-3-week dosing (ranging from 60 to 75 mg/m^2 every 3 weeks; n = 21), all with concomitant prednisone. Patients who were concurrently treated with carboplatin or investigational therapies in addition to docetaxel were not included in this analysis. The duration of docetaxel therapy was per individual treating physician. Reasons for treatment discontinuation were assessed retrospectively.

Each patient had signed an institutional review board (IRB)-approved, protocol-specific informed consent form in accordance with federal and institutional guidelines before initiating treatment with AA. The subsequent retrospective review of outcomes after docetaxel therapy was IRB-approved.

Statistical Methods and Data Analysis

Retrospective data collected included baseline patient characteristics at the start of docetaxel therapy such as validated prognostic factors in mCRPC, baseline PSA, Gleason score at the time of diagnosis, presence of visceral metastases, and use of opioid analgesics for cancer-associated pain.[16] The maximal PSA percent decline from baseline was determined using all known serum PSA determinations obtained during therapy. Patients were categorized as experiencing PSA declines $\geq$ 30% and $\geq$ 50% from baseline if confirmed using repeat PSA measurement at least 4 weeks after the initial measurement, consistent with PCWG2 guidelines.[15] The Kaplan-Meier product limit method was used to estimate the median overall survival from the date of first dose of docetaxel.[17] Patients were censored at the date last known alive for the analysis of overall survival.

Patients were subdivided into those with primary versus acquired AA resistance. Acquired AA resistance was defined as patients who experienced a PSA decline > 50% from baseline or radiographically stable disease for $\geq$ 8 months, with subsequent disease progression with AA. All other patients were defined as having primary AA resistance. Outcomes after docetaxel therapy according to subgroups of patients with primary or acquired resistance to AA were assessed using descriptive statistics. No formal statistical comparisons were performed between subgroups.

Results

Outcomes With Previous AA Therapy and Baseline Patient Characteristics

Twenty-three patients who experienced disease progression while taking AA and were subsequently treated with docetaxel between 2007 and 2013 were included in this retrospective analysis, including 11 (48%) treated with AA in the phase III randomized study (subsequent unblinding of phase III treatment allocation allowed identification of patients with previous AA therapy). The distribution of AA dosing is shown in Table 1. Fifteen patients (65%) were treated at the standard dosing of AA (1000 mg/d in a modified fasting state with prednisone 5 mg twice daily). Outcomes for AA therapy are shown in Table 1. Twelve patients (52%) experienced a $\geq$ 50% decline from baseline in serum PSA with AA treatment. Fifteen patients (65%) discontinued AA because of radiographic or clinical progression and 8 (35%) because of PSA progression; the median