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Original article

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-