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Outcomes with Abiraterone Acetate in Metastatic Castration-resistant Prostate Cancer Patients Who Have Poor Performance Status

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Abstract

Background: Although abiraterone acetate (abiraterone) has proven efficacy in two randomised phase 3 trials in metastatic castration-resistant prostate cancer (mCRPC), patients who had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥2 were either excluded or under-represented in these trials.
Objective: To compare outcomes in ECOG PS 0–1 and ≥2 in mCRPC patients treated with abiraterone.
Design, setting, and participants: Cancer registries from three Canadian centres were used to retrospectively identify mCRPC patients (postdocetaxel and docetaxel-naïve) treated with abiraterone. ECOG PS, clinicopathologic characteristics, prostate-specific antigen (PSA) response, and survival data were collected.
Outcome measurements and statistical analysis: Survival outcomes were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards modelling was used to examine the effect of clinicopathologic characteristics on overall survival (OS) and time to PSA progression.
Results and limitations: A total of 519 patients were identified; 61% (n = 318) and 39% (n = 201) were ECOG PS 0–1 and ≥2, respectively. ECOG PS 0–1 patients were significantly more likely than PS ≥2 patients to achieve a PSA decline ≥50% from baseline (45% vs 32%; p = 0.003, Fisher exact test) and had significantly longer median time to PSA progression (5.2 mo vs 4.1 mo; p = 0.023), median treatment duration (7.4 mo vs 4.5 mo; $p < 0.001$), and median OS (20.0 mo vs 9.1 mo; $p < 0.001$). On multivariate analysis, ECOG PS was a significant factor for OS ($p < 0.001$), time to PSA progression (p = 0.043), and PSA decline (p = 0.002). Potential limitations include the retrospective study design and subjective nature of ECOG PS classification.
Conclusions: ECOG PS ≥2 mCRPC patients treated with abiraterone have inferior outcomes compared with ECOG 0–1 patients, especially in regard to OS. These data indicate that early initiation of abiraterone prior to a decline in PS may be warranted.
Patient summary: We found that advanced prostate cancer patients who have worse performance status (PS) derive less benefit from abiraterone, indicating that earlier treatment before PS declines could improve outcomes.

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1. Introduction

The therapeutic armamentarium for metastatic castration-resistant prostate cancer (mCRPC) has rapidly expanded in recent years [1,2]. Among the agents now available to treat mCRPC is abiraterone acetate (abiraterone), a novel, orally available inhibitor of CYP17, an enzyme centrally involved in extragonadal androgen synthesis [3]. In phase 3 randomised trials in mCRPC, abiraterone improves radiographic progression-free survival in docetaxel-naïve patients (COU-AA-302 trial) [4] and overall survival (OS) in patients previously treated with docetaxel (COU-AA-301 trial) [5]. The COU-AA-302 trial was restricted to Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1 patients, while in the COU-AA-301 study, only 10% of enrolled patients were ECOG PS 2. Thus, the activity of abiraterone in ECOG PS $\geq$2 patients is not well described, which may have important implications for the generalizability of the COU-AA-301 and COU-AA-302 trials, because in clinical practice, abiraterone is commonly used in ECOG PS $\geq$2 patients [6]. Using an unselected cohort from three large cancer centres in Canada, the aim of this retrospective study was to compare the efficacy of abiraterone in ECOG PS $\geq$2 and 0–1 patients.

2. Patients and methods

2.1. Patient population

Cancer registries at the British Columbia Cancer Agency (BCCA) Alberta Health Services–Cancer Care (AHS-CC) and Princess Margaret Cancer Centre (PM) were reviewed to identify mCRPC patients treated with abiraterone. A total of 519 eligible patients were identified—325 at BCCA, 78 at AHS-CC, and 116 at PM. ECOG PS at initiation of abiraterone was recorded as per assessment of the treating clinician. Patient demographics, prior treatments, and clinicopathologic characteristics were also documented from the medical records of each patient. Research ethics board approval was obtained at all sites. Data were transferred between centres in a deidentified manner.

2.2. Outcomes

For each patient, prostate-specific antigen (PSA) response and modes of progression on abiraterone (PSA, measurable, clinical) were recorded. PSA and measurable progression were classified as per Prostate Cancer Working Group 2 criteria [7], while *clinical progression* was defined as worsening disease-related symptoms (pain, fatigue, anorexia or weight loss, or urinary symptoms) necessitating a change in antineoplastic therapy (eg, use of palliative bone radiation therapy or institution of new systemic therapy) or a decrease in ECOG PS $\geq$2 levels. *Overall survival* was defined as the time from initiation of abiraterone to death of any cause or censoring on 1 November 2013.

2.3. Statistics

Baseline clinicopathologic characteristics in ECOG PS 0–1 and $\geq$2 patients were compared using the Fisher exact test and Student t test. Time to PSA progression, treatment duration, and OS were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards modelling was used to examine the effect of baseline characteristics on OS and time to PSA progression. Multivariate logistic regression was used to examine the correlation between baseline characteristics and PSA decline $\geq$50%.

Multivariate survival analysis was performed with a prognostic index recently developed from a post hoc analysis of the COU-AA-301 trial [8]. Development of this index involved the following steps: (1) Important clinicopathologic factors were identified and dichotomised for high and low values, as needed; (2) baseline clinicopathologic factors were assessed for association with OS using a univariate Cox proportional hazards model; (3) factors that were significant on univariate analysis were incorporated in a step-wise procedure into a multivariate Cox proportional hazards regression model; (4) factors that were significant on multivariate analysis were incorporated into the final model, which was subject to validation by a bootstrapping approach; (5) the C-index was used to assess the accuracy of the model, which consisted of six factors; and (6) patients were categorised into risk groups based on the number of baseline risk factors with median OS calculated for each risk group.

3. Results

3.1. Patient population

Baseline clinicopathologic characteristics stratified by ECOG PS are presented in Table 1. The following factors significantly differed between ECOG PS 0–1 and $\geq$2 patients: median time from commencement of androgen depravation therapy (ADT) to starting abiraterone, serum lactate dehydrogenase (LDH), serum alkaline phosphatase (ALP), and serum albumin. There was also a strong trend towards higher rates of visceral metastases in ECOG PS $\geq$2 patients, although the difference did not reach statistical significance, which may be accounted for by the relatively small total number of patients who had visceral metastases (n = 81). The proportion of patients who had received prior docetaxel did not differ between the two groups.

3.2. Treatment outcomes

As of 1 November 2013, 410 (79%) patients had ceased abiraterone treatment. In these patients, 391 (95%), 266 (65%), and 150 (29%) had PSA, clinical, and objective disease progression, respectively (more than one mode of progression could apply for any one patient). Treatment outcomes with abiraterone in ECOG PS 0–1 and $\geq$2 patients are presented in Table 2. ECOG PS 0–1 patients were significantly more likely to attain a PSA decline $\geq$50% and had significantly longer median time to PSA progression, median treatment duration, and median OS (Fig. 1A). Notably, an OS benefit for ECOG PS 0–1 patients was seen in both postdocetaxel (19.2 mo vs 8.7 mo; Fig. 1B) and docetaxel-naïve patients (26.0 mo vs 10.3 mo; Fig. 1C). No significant difference was seen in the proportion of ECOG PS $\geq$2 and 0–1 patients who had PSA (72% vs 77%; p = 0.21) or objective disease progression (25% vs 31%; p = 0.31), but clinical progression was significantly more frequent in the ECOG PS $\geq$2 cohort (63% vs 44%; $p < 0.001$).

3.3. Postabiraterone treatment

A total of 207 patients (40%) patients received at least one systemic agent after abiraterone, with 57 receiving more