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Low Incidence of Corticosteroid-associated Adverse Events on Long-term Exposure to Low-dose Prednisone Given with Abiraterone Acetate to Patients with Metastatic Castration-resistant Prostate Cancer

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Abstract

Background: Abiraterone acetate (AA) is the prodrug of abiraterone, which inhibits CYP17A1 and testosterone synthesis and prolongs the survival of patients with metastatic castration-resistant prostate cancer (mCRPC). AA plus prednisone (P) (AA + P) is approved for the treatment of patients with mCRPC.
Objective: To investigate whether long-term use of low-dose P with or without AA leads to corticosteroid-associated adverse events (CA-AEs) in mCRPC patients.
Design, setting, and participants: The study included 2267 patients in COU-AA-301 and COU-AA-302. We used an inclusive Standardized MedDRA Queries–oriented approach to identify 112 preferred terms for known CA-AEs, and assessed the incidence of CA-AEs during 3-mo exposure intervals and across all P exposure levels.
Intervention: All 2267 patients received 5 mg of P twice daily, and 1333/2267 received AA (1 g) plus P.
Results and limitations: The CA-AE incidence after any P exposure was 25%, 26%, and 23% for any grade, and 5%, 5%, and 4% for grade ≥3 CA-AEs for all patients and the AA + P and P alone groups, respectively. The most common any-grade CA-AEs were hyperglycemia (7.4%, 7.8%, and 6.9% for all patients, AA + P, and P alone, respectively) and weight increase (4.3%, 3.9%, and 4.8%, respectively). When assessed by duration of exposure (3-mo intervals up to ≥30 mo), no discernable trend was observed for CA-AEs, including hyperglycemia and weight increase. The investigator-reported study discontinuation rate due to CA-AEs was 11/2267 (0.5%), and one patient had a CA-AE resulting in death.

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Conclusions: Low-dose P given with or without AA is associated with low overall incidence of CA-AEs. The frequency of CA-AEs remained low with increased duration of exposure to P.
Patient summary: We assessed adverse events in patients with metastatic castration-resistant prostate cancer during long-term treatment with a low dose of a corticosteroid. We found that long-term treatment with this low-dose corticosteroid is safe and tolerable.

1. Introduction

Abiraterone acetate (AA) is the prodrug of abiraterone, which selectively blocks CYP17. CYP17 is required for androgen biosynthesis, which occurs in testicular, adrenal, and prostatic tumor tissue [1–3]. AA plus prednisone (P) (AA + P) is approved for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) on the basis of a demonstrated survival benefit and a favorable tolerability profile in both prechemotherapy and postchemotherapy settings [4–8]. In the final analysis of the phase 3 COU-AA-301 trial of postchemotherapy patients with mCRPC, AA + P significantly prolonged median overall survival (OS) by 4.6 mo (26% reduction in risk of death compared with placebo plus P, hereafter denoted P alone) [4,5]. Compared with P alone, AA + P significantly prolonged OS by 4.4 mo (19% reduction in risk of death) in the final analysis of the phase 3 COU-AA-302 trial of prechemotherapy patients with mCRPC [6–8].

Corticosteroids may be used by patients with cancer, including those with mCRPC, to manage cancer-related pain and weight loss and the side effects of chemotherapy [9,10]. Long-term use of moderate or high corticosteroid doses (eg, ≥20 mg/d P) has an established adverse event (AE) profile [11,12]. A list of common corticosteroid-associated AEs (CA-AEs) is presented in Section 2. There are some concerns about whether the frequency and severity of side effects would be similar for long-term coadministration of AA and low-dose P. To address this question, we used the COU-AA-301 and COU-AA-302 data sets to investigate whether long-term use of low-dose P with or without AA in patients with mCRPC leads to CA-AEs.

2. Patients and methods

The design, eligibility criteria, and efficacy results for the COU-AA-301 (NCT00638690) and COU-AA-302 (NCT00887198) phase 3 trials have been described previously [4–8]. In brief, COU-AA-301 and COU-AA-302 randomized post-docetaxel and chemotherapy-naïve mCRPC patients 2:1 and 1:1 to AA (1 g) plus P or to P alone (5 mg twice a day [BID]), respectively [4–8]. A total of 1195 patients were enrolled in COU-AA-301 (AA + P, $n = 797$; P alone, $n = 398$) [4,5] and 1088 patients in COU-AA-302 (AA + P, $n = 546$; P alone, $n = 542$) [6–8]. The combined total of 2267 patients in COU-AA-301 and COU-AA-302 were included in the safety population and received 5 mg BID P. Of these, 1333 patients received AA + P.

We used an inclusive Standardized MedDRA Queries–oriented approach to identify 116 preferred terms for known CA-AEs according to the P label to interrogate the COU-AA-301 and COU-AA-302 databases. Irrelevant preferred terms were excluded, and upcoding strategies were applied to convert and match with legacy MedDRA versions (version 17 used for these analyses). CA-AEs of interest were as follows:

1. **Endocrine disorders:** adrenal insufficiency, Cushing's syndrome, Cushingoid state, pituitary-dependent Cushing's syndrome
2. **Eye disorders:** cataract, cataract cortical, cataract subcapsular
3. **Gastrointestinal disorders:** chronic gastrointestinal bleeding, duodenal perforation, duodenal ulcer, duodenal ulcer hemorrhage, duodenal ulcer perforation, duodenal ulcer perforation (obstructive), duodenal ulcer (obstructive), duodenitis (hemorrhagic), erosive duodenitis, erosive esophagitis, feces discolored, gastric hemorrhage, gastric perforation, gastric ulcer, gastric ulcer hemorrhage, gastric ulcer hemorrhage (obstructive), gastric ulcer perforation, gastric ulcer perforation (obstructive), gastritis (erosive), gastritis (hemorrhagic), gastroduodenal hemorrhage, gastroduodenal ulcer, gastroduodenitis (hemorrhagic), gastrointestinal erosion, gastrointestinal hemorrhage, gastrointestinal perforation, gastrointestinal ulcer, gastrointestinal ulcer hemorrhage, gastrointestinal ulcer perforation, hematemesis, hematochezia, hemorrhagic erosive gastritis, jejunal ulcer, jejunal ulcer perforation, melena, esophageal hemorrhage, esophageal perforation, esophageal ulcer, esophageal ulcer hemorrhage, esophageal ulcer perforation, esophageal varices hemorrhage, esophagitis (hemorrhagic), esophagitis (ulcerative), peptic ulcer, peptic ulcer hemorrhage, peptic ulcer perforation, peptic ulcer perforation (obstructive), peptic ulcer (obstructive), proctitis (hemorrhagic), upper gastrointestinal hemorrhage
4. **General disorders and administration site conditions:** impaired healing, perforated ulcer
5. **Infections and infestations:** peptic ulcer *Helicobacter*
6. **Injury, poisoning, and procedural complications:** acetabulum fracture, atypical femur fracture, cervical vertebral fracture, femoral neck fracture, forearm fracture, hip fracture, lumbar vertebral fracture, rib fracture, spinal compression fracture, thoracic vertebral fracture, wrist fracture
7. **Investigations:** blood glucose abnormal, blood glucose fluctuation, blood glucose increased, body mass index increased, bone density decreased, gastric occult blood positive, glucose tolerance decreased, glucose tolerance test abnormal, glucose urine present, glycosylated hemoglobin increased, occult blood positive, weight increase
8. **Metabolism and nutrition disorders:** abnormal weight gain, central obesity, diabetes mellitus, diabetes mellitus inadequate control, glucose tolerance impaired, hyperglycemia, impaired fasting glucose, insulin-requiring type 2 diabetes mellitus, metabolic syndrome
9. **Musculoskeletal and connective tissue disorders:** bone formation decreased, bone loss, myopathy, myopathy toxic, osteopenia, osteoporosis, osteoporotic fracture, resorption bone increased, spinal deformity
10. **Renal and urinary disorders:** glycosuria
11. **Skin and subcutaneous disorders:** ecchymosis, hemorrhage (subcutaneous), hemorrhage (subepidermal), purpura, skin atrophy, skin fragility, skin hemorrhage, skin striae
12. **Surgical and medical procedures:** cataract operation, duodenal ulcer repair, gastrointestinal ulcer management, perforated peptic ulcer oversewing

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