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Original Article

Early abiraterone acetate treatment is beneficial in Japanese castration-resistant prostate cancer after failure of primary combined androgen blockade

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ABSTRACT

Background: Development of novel agents targeting the androgen axis has led to improved overall survival in castration-resistant prostate cancer (CRPC). This study aimed to investigate the optimal timing of treatment with one such agent, abiraterone acetate (AA), in Japanese patients.

Materials and methods: Between July 2014 and February 2016, 106 CRPC patients were administered AA in Nagoya City University Hospital, Nagoya, Japan and in four affiliated hospitals following failure of primary combined androgen blockade (CAB). Of these, records of 69 patients treated before chemotherapy were retrospectively analyzed. Patients were divided into two AA treatment groups: (1) first- or second-line after diagnosis of CRPC, designated the Early Group, and (2) third-line onwards, designated the Deferred Group. Prostate-specific antigen (PSA) response rate, $\geq$ 50% PSA decline rate with treatment, progression-free survival (PFS), and overall survival (OS) were compared between the two groups. National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 was used to classify adverse events.

Results: In 24 patients in the Early Group and 45 patients in the Deferred Group, no significant differences in baseline parameters were observed between groups. PSA response rate, $\geq$ 50% PSA decline rate and PFS (but not OS) were significantly better in the Early Group than in the Deferred Group. Serum aspartate aminotransferase/alanine aminotransferase elevations were the most common Grade 3 treatment-related toxicities, and were clinically manageable. In subgroup analyses of the Early Group, comparison of first-line AA with second-line AA after flutamide treatment showed no changes in PSA response rate, PFS, or OS.

Conclusion: This study suggests improved favorable outcomes of first- or second-line AA treatment in Japanese chemotherapy-naïve CRPC patients after failed CAB; statistical confirmation of such improvement was evident for PFS, but not OS. In addition, early AA treatment exhibited an acceptable safety profile.

1. Introduction

Changes in lifestyle such as adoption of Western diets are possible contributing factors to the gradually observed increase in prostate cancer incidence and mortality in the Japanese population.[1–3] Androgen deprivation therapy (ADT) remains the main first-line treatment for metastatic prostate cancer patients.

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However, the benefits of such treatment are short-lived, persisting only for a few years, by which time the disease undergoes transformation into metastatic castration-resistant prostate cancer (CRPC). Nonetheless, the development of several new drugs targeting the androgen axis has led to improvement in overall survival.[4–6]

Abiraterone acetate (AA) is one such new agent that selectively inhibits androgen synthesis in testes, adrenal glands, and tumor tissues by inhibition of cytochrome P450. AA has been approved in > 70 countries including Japan (in 2014) for treatment of chemotherapy-naïve metastatic CRPC patients and clinical studies have demonstrated its efficacy and safety.[7–9]

In accordance with Western guidelines such as those of the National Comprehensive Cancer Network (NCCN)[10] and European Association of Urology (EAU),[11] AA has been recommended as first-line treatment in metastatic CRPC patients after primary ADT. However, there are differences in approach between Western and Asian countries with regard to primary ADT. The NCCN and EAU guidelines do not generally recommend primary ADT for non-metastatic prostate cancer patients, except in very high-risk disease, whereas Japanese guidelines include primary ADT as an option for all males except cases at very low risk. Furthermore, in Japan, combined androgen blockade (CAB) using antiandrogens such as bicalutamide and luteinizing hormone releasing hormone analogs has prevailed widely on the basis of several large multicenter randomized studies.[12–16] In addition, vintage hormonal manipulation switching from bicalutamide to flutamide has frequently prevailed. Therefore, the present study sought to establish the optimal timing of treatment with AA in Japanese CRPC patients following failure of CAB. This was achieved by retrospective analysis of the efficacy and safety of AA use before chemotherapy in a multi-institutional context.

2. Materials and methods

2.1. Patients and treatment evaluation

A review was undertaken of 106 CRPC patients treated with oral AA (1,000 mg once daily) + prednisolone (5 mg twice daily) in five centers, including Nagoya City University Hospital, Nagoya, Japan, between July 2014 and February 2016. With Institutional Review Board approval in Nagoya City University Hospital, approved number was 60160035, the medical records of these patients were retrospectively analyzed. Sixty-nine of this cohort treated before chemotherapy were enrolled in the study. All patients had a histological diagnosis of prostate adenocarcinoma, which had progressed despite achieving castration-level values for testosterone by primary CAB treatment using a combination of oral bicalutamide 80 mg once daily and luteinizing hormone-releasing hormone agonist.

Clinical, biochemical, or radiographic progressive disease was defined according to Prostate Cancer Clinical Trials Working Group criteria.[17] Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. The following variables were recorded following consultation of electronic patient medical records: patient age, initial prostate-specific antigen (PSA) levels, number of metastatic sites, prostate biopsy Gleason score, PSA response which was defined as the improvement of PSA levels at 12 weeks after AA treatment, absence/presence of PSA flare, nadir PSA level, and free survival (PFS) was measured from the start of the AA treatment until the time of radiographic or PSA progression. Patients were divided into two AA treatment groups: (1) first- or second-line following flutamide switching after diagnosis of free survival (PFS) was measured from the start of the AA treatment until the time of radiographic or PSA progression. Patients were divided into two AA treatment groups: (1) first- or second-line following flutamide switching after diagnosis of CRPC, designated the Early Group, and (2) third-line onwards, designated the Deferred Group. Statistical comparisons were made between these two groups. Clinical characteristics of all patients are listed in Table 1.

2.2. Statistical analysis

Differences in categorical parameters were assessed using the Student t test. Cumulative rates were estimated using the Kaplan–Meier method, and the significance of differences between curves was tested by the log-rank test. Univariate and multivariate analyses employed the Cox proportional hazard regression model. A value of $P < 0.05$ was considered statistically significant. All data were analyzed using EZR software (Saitama Medical Center, Jichi Medical University, Yakushiji, Japan).

3. Results

3.1. Baseline population profile

Patient numbers in the Early and Deferred Groups, median ages of patients, and median initial PSA levels are shown in Table 1. Gleason score obtained by prostate needle biopsy was > 8 in all patients; most of whom also exhibited bone metastasis (approximate incidence almost 1 per site per group). There were no significant differences in clinical profile between the groups for initial diagnosis of CRPC. Median follow-up period from the diagnosis of CRPC was 15.3 (4.8–31.5) months in the Early Group and 40.8 (9.5–177.8) months in the Deferred Group, respectively.

3.2. Clinical response and outcomes of AA treatment

OS did not differ between the groups (Figs. 1A, 1B). Waterfall plot at the maximum PSA changes is shown in Fig. 2. As can be seen, the majority of patients had a decline in PSA level during this treatment period in the Early Group. Univariate and multivariate analyses of baseline parameters revealed that early use of AA was the only prognostic factor for PFS (Table 2).

In subgroup analyses in the Early Group, all patients receiving second-line AA treatment after diagnosis of CRPC had previously been treated with flutamide as first-line therapy; therefore, the first-line group ($n = 9$) and those receiving second-line AA treatment after flutamide ($n = 15$) were analyzed. As shown in Table 3, baseline profiles did not differ significantly. In addition, there were no significant differences in PSA response or $\geq$ 50% PSA decline rates. Furthermore, PFS and OS did not differ significantly between the two groups (Figs. 3A, 3B).

3.3. Adverse events

Table 4 shows the treatment-related extent of toxicity in all 69 patients treated with AA. In this cohort of chemotherapy-naïve patients, hepatic dysfunction, hypokalemia, and thrombocytopenia were Grade 3 adverse events. These analyses did not reveal any incidence of Grade 4 toxicity or treatment-related death.

4. Discussion

CAB with agents such as bicalutamide and luteinizing hormone-releasing hormone (LHRH) analogs has proved ineffective in CRPC patients. The present retrospective multi-institutional analysis of AA efficacy has demonstrated the benefit of first- or second-line AA treatment, as indicated by reductions in the PSA response and increases in PFS; AA also exhibited an acceptable safety profile. In the

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