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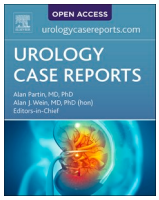

Oncology

AKR1C3-negative high-risk metastatic castration-sensitive prostate cancer has long-term response to first-line treatment with abiraterone: Four case reports

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ABSTRACT

We experienced four cases of high-risk metastatic castration-sensitive prostate cancer (mCSPC) in which first-line treatment with abiraterone showed a sustained long-term response of over 5 years. We conducted immunohistochemical staining of aldo-keto reductase family 1 member C3 (AKR1C3) expression, which associate with poor prognosis of metastatic castration-resistant prostate cancer (mCRPC), and all prostate cancer tissue from four cases showed negative. These results suggested that AKR1C3-negative high-risk mCSPC cases may respond well to first-line treatment with abiraterone. This is the first report describing association of high-risk mCSPC and negative AKR1C3.

1. Introduction

Immunohistochemical staining of prostate cancer tissue from metastatic castration-resistant prostate cancer (mCRPC) showed that the expression of aldo-keto reductase family 1 member C3 (AKR1C3) was closely associated with mCRPC treatment resistance to abiraterone.[1] However, AKR1C3 expression in metastatic castration-sensitive prostate cancer (mCSPC) and the effectiveness of abiraterone as a first-line treatment have not yet been investigated. Here, we report four cases of AKR1C3-negative high-risk mCSPC in which first-line treatment with abiraterone showed sustained long-term responses of over 5 years.

2. Case presentation

Case 1 was an 82-year-old patient with a previous history of low back pain and a performance status (PS) of 1. Initial prostate-specific antigen (iPSA) level was 1892 ng/mL, so he underwent prostate biopsy (six locations) in March 2018 which revealed adenocarcinoma in six locations with Gleason score of 4 + 5 = 9. Contrast-enhanced computed tomography (CECT) showed multiple lymph node metastases, the bone scan showed metastases in 44 locations. A diagnosis of cT4N1M1b was made, and in March 2018, he began a first-line treatment of androgen deprivation therapy (ADT) + abiraterone 1000 mg daily + predonisolone 5 mg daily. PSA levels were <0.2 ng/mL after 12 months, <0.1 ng/mL after 15 months, <0.04 ng/mL after 24 months (Fig. 1). The patient showed a 72-month durable response.

Case 2 was an 83-year-old patient with a previous history of diabetes and PS of 1. iPSA level was 1336 ng/mL, so he underwent a prostate biopsy (12 locations) in June 2018 which revealed adenocarcinoma in 12 locations with Gleason score of 4 + 4 = 8. CECT showed multiple lymph node metastases, the bone scan showed metastases in 13 locations. A diagnosis of cT4N1M1b was made, and in June 2018, he began a first-line treatment of ADT + abiraterone 1000 mg daily + predonisolone 5 mg daily. PSA levels were <0.1 ng/mL after 3 months, <0.04 ng/mL after 4 months (Fig. 1). The patient showed a 69-month durable response.

Case 3 was a 60-year-old patient with no previous history and a PS of 0. iPSA level was 649.8 ng/mL, so he underwent a prostate biopsy (12 locations) in August 2018 which revealed adenocarcinoma in seven locations with Gleason score of 4 + 5 = 9. CECT showed multiple lymph node metastases, the bone scan showed metastases in 23 locations. A diagnosis of cT3bN1M1b was made, and in August 2018, he began a first-line treatment of ADT + abiraterone 1000 mg daily + predonisolone 5 mg daily. PSA levels were <0.2 ng/mL after 5 months,

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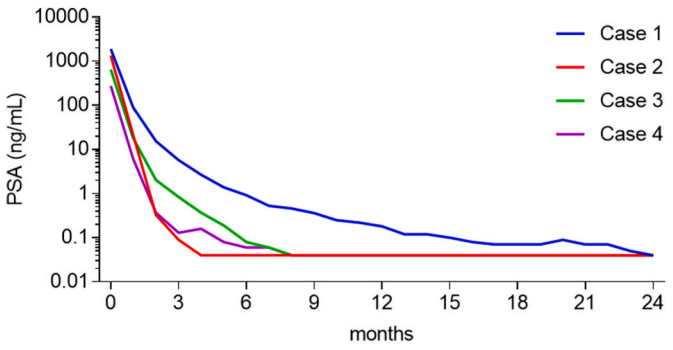

Fig. 1. Shifts in prostate-specific antigen levels from before treatment to 24 months after treatment in four cases.

<0.1 ng/mL after 6 months, <0.04 ng/mL after 8 months (Fig. 1). The patient showed a 67-month durable response.

Case 4 was an 82-year-old patient with a previous history of low back pain and a PS of 1. iPSA level was 276.2 ng/mL, so he underwent a prostate biopsy (four locations) in November 2018 which revealed adenocarcinoma in four locations with Gleason score of 4 + 5 = 9. CECT showed multiple lymph node metastases, the bone scan showed metastases in 10 locations. A diagnosis of cT4N1M1b was made, and in November 2018, he began a first-line treatment of ADT + abiraterone 1000 mg daily + predonisolone 5 mg daily. PSA levels were <0.2 ng/mL after 3 months, <0.1 ng/mL after 5 months, <0.04 ng/mL after 8 months (Fig. 1). The patient showed a 64-month durable response.

Additionally, the BONENAVI-based Bone Scan Index (BSI) and Hotspot number (Hsn) decreased over time for all four cases (Fig. 2). Furthermore, we conducted immunohistochemical staining of the prostate cancer tissues of these four cases and assessed AKR1C3 expression. However, all four cases were negative (Fig. 3).

3. Discussion

The LATITUDE trial reported in 2017 confirmed that overall survival (OS) and radiographic progression-free survival (rPFS) were significantly prolonged when combined treatment of ADT with abiraterone and prednisone was conducted for high-risk mCSPC cases with at least two of the following: Gleason score of ≥8, ≥3 bone lesions on a bone scan, and visceral metastasis.[2] Specifically, the OS rate was 66% in the abiraterone group vs. 49% in the control group, and the median rPFS was 33 months in the abiraterone group vs. 14.8 months in the control group.[2] Based on these results, abiraterone became covered by insurance in Japan in 2018 for high-risk mCSPC cases that have not been treated with endocrine therapy. Matsubara et al.[3] reported in a post hoc analysis of the LATITUDE trial that patients who achieved PSA<0.1 ng/mL 6 months after starting treatment had favorable OS and rPFS. In our case group, we achieved a recurrence-free and progression-free period of

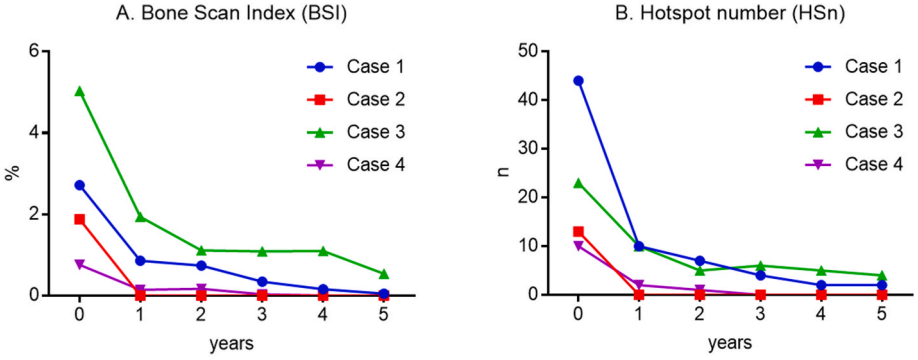

Fig. 2. Shifts in BONENAVI-based Bone Scan Index (BSI) (A) and Hotspot number (HSn) (B) for four cases.

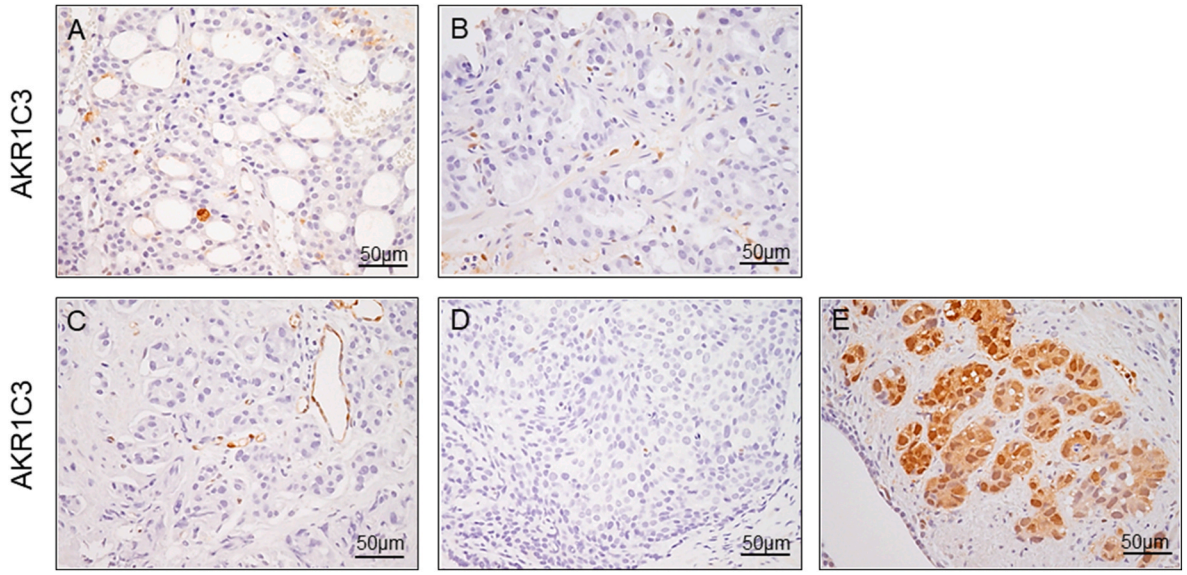

Fig. 3. Immunohistochemical staining of AKR1C3 using prostate cancer tissue. Representative images of the present AKR1C3-negative case group (A–D) and positive control case (E) are shown.

over 5 years, significantly exceeding the results of the above-mentioned clinical trial. Three out of four cases achieved PSA<0.1 ng/mL by 6 months after starting treatment. Meanwhile, the remaining case also achieved PSA<0.1 ng/mL after 15 months and PSA<0.04 ng/mL after 24 months. Although the sample size is small and limited, in cases where the PSA nadir was <0.04 ng/mL, first-line treatment with abiraterone may result in a long-term response that exceeds the results of clinical trials.

Zhao et al.[1] reported AKR1C3 expression associated with early treatment resistance to abiraterone. We have experienced three cases of high-risk mCSPC that started first-line treatment with abiraterone at the same time as the four cases reported in this paper and that developed early treatment resistance within 1 year. None of these three cases reached PSA<0.2 ng/mL, and all prostate cancer tissues were positive for AKR1C3 at the time of diagnosis (Data not shown).

AKR1C3 is one of the key enzymes that catalyzes the conversion of androstenedione to testosterone. Furthermore, it promotes the conversion of 5α' androstenedione and androsterone, which are metabolic pathways not inhibited by abiraterone, to testosterone and DHT, respectively, which are more active androgens.[4] AKR1C3 is overexpressed in abiraterone-resistant prostate cancer cells, and down-regulation of AKR1C3 improves treatment resistance to abiraterone.[4]

Androgen receptor (AR) variants and *SPOP* mutations have previously been reported as markers associated with abiraterone treatment sensitivity.[5] However, these reports mainly used cases of castration-resistant prostate cancer (CRPC), and the results are controversial. In all four cases, the prostate cancer tissue at the time of diagnosis was negative for AKR1C3, suggesting that this is a very promising marker for the long-term effectiveness of abiraterone.

Furthermore, indomethacin suppresses AKR1C3. It inhibits intracrine androgen levels, suppresses AR and AR mutant expression, and overcomes abiraterone resistance both *in vitro* and *in vivo*.[4] Therefore, clinical trials of AKR1C3 inhibitors and the development of new AKR1C3 inhibitors are expected in the future.

4. Conclusion

First-line treatment with abiraterone may have a long-term response in high-risk mCSPC cases in which prostate cancer tissue is negative for AKR1C3 and PSA<0.04 ng/mL.

Informed consent

Informed consent for publication of the present case details was obtained from the patient.

CRediT authorship contribution statement

Tsuyoshi Yoshizawa: Conceptualization, Data curation, Investigation, Writing – original draft. **Yoko Nakanishi:** Investigation, Visualization. **Daisuke Obinata:** Methodology, Visualization. **Kenya Yamaguchi:** Project administration, Writing – review & editing. **Shinobu Masuda:** Supervision. **Satoru Takahashi:** Supervision.

Declaration of competing interest

The authors declare no conflict of interest.

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