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Delayed Antiandrogen Withdrawal Syndrome After Discontinuation of Bicalutamide

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Introduction

Prostate cancer is the most common solid tumor malignancy in men, in the United States, accounting for 233,000 new cases and 29,480 deaths in 2013¹. Inhibition of gonadal androgen synthesis, with or without androgen receptor (AR) blockade with an oral antiandrogen, is the mainstay of treatment for metastatic hormone-sensitive prostate cancer. Although most patients will initially respond to androgen deprivation therapy (ADT), responses are not durable, with median response duration of about 18 months². Metastatic castration-resistant prostate cancer (mCRPC), the terminal stage of this disease, has an overall survival between 2-3 years^{3, 4}. Common therapies include chemotherapy, targeted endocrine therapies, radiopharmaceuticals, and immunotherapy⁵. Prior to further therapies, if patients are on combined androgen blockade (CAB), the first maneuver is withdrawal of the antiandrogen with continuation of luteinizing hormone releasing hormone therapy.

Kelly and Scher published an early description of withdrawal of an oral antiandrogen as a therapeutic maneuver in 1993⁶. Since then, multiple case series, a randomized trial including ketoconazole, and a larger clinical trial have confirmed the clinical response to antiandrogen

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withdrawal (AAW) in patients who have progressed on CAB⁶⁻¹⁶. Clinical responses, observed either as a prostate-specific antigen (PSA) decline or improvement in symptoms, are noted between 1 and 6 weeks after discontinuation of the antiandrogen, depending on the half-life of the agent^{6-12, 15, 16}. In the largest clinical trial, the median duration of response was 3 months.

The recommended period of waiting for an AAW response of 4-6 weeks is based on the pharmacology of the antiandrogen and the half-life of PSA. The half-lives of flutamide, nilutamide, and bicalutamide are 7.8 hours, 56 hours, and 1 week, respectively¹⁷⁻¹⁹. Therefore, the time required to endure 4 half-lives for washout from the serum would be 31.2 hours, 9.3 days, and 4 weeks, respectively. The half-life of PSA in the serum is 2-3 days, resulting in an estimate 1 to 6 weeks for PSA to decline after AAW. Prior research has estimated that the AAW response, as measured by rates of PSA decline, occurs in 11 to 33% of patients undergoing antiandrogen withdrawal^{8, 12, 15, 16, 20, 21}. To avoid misattribution of clinical benefit to a subsequent agent when commencing a new therapy immediately following AAW, clinical trials in mCRPC generally mandate a minimum 4-6 week AAW period before enrollment to ensure that a PSA decline does not occur²².

We report a series of patients who underwent AAW after PSA progression on CAB while awaiting enrollment in a clinical trial. All patients had a delayed and unexpected AAW response even after continued PSA rises at 6 weeks after antiandrogen discontinuation. Appropriate institutional review board approval was obtained to describe this phenomenon.

Case 1

A 79-year-old man presented initially with low back pain and was found to have a PSA elevated to 130.09 ng/mL. Further evaluation disclosed diffuse metastatic prostate cancer involving the bones and lymph nodes. He was begun initially on CAB with leuprolide and bicalutamide, and elected to participate in a clinical trial, SWOG 0925. He was randomized to CAB with cixutumumab, and he completed this trial after 7 months of treatment with a PSA decline to undetectable. CAB alone was continued after the 7-month course of cixutumumab was completed.

At approximately 1 year and 8 months after commencing CAB, his PSA began to rise, from undetectable levels to 0.04 ng/mL, then to 0.64 ng/mL 3 months later. Bicalutamide was withdrawn, yet his PSA increased from 1.85 to 4.15 ng/mL in a period of 44 days — while waiting to enroll in a clinical trial — then declined to 1.34 ng/mL after 74 days and undetectable after 89 days (Figure 1A). His PSA has remained undetectable for the past 16 months without other evidence of disease progression.

Case 2

A 65-year-old man presented with right hip and leg pain and was found to have a PSA of 4260 ng/mL. A biopsy and imaging studies disclosed Gleason 4+5=9, metastatic adenocarcinoma of the prostate. He commenced treatment with bicalutamide and one month later leuprolide was added, with rapid resolution of pain. His PSA dropped to 2.07 ng/mL after 7 months of CAB, and eventually reached a nadir of 0.54 ng/mL after fifteen months.

Two years after starting CAB, his PSA rose to 4.22 ng/mL, marking mCRPC. Bicalutamide was withdrawn, but his PSA continued to climb to 6.7 ng/mL, 32 days after and 7.1 ng/mL, 40 days after discontinuation of bicalutamide (Figure 1B). Despite the rise in PSA, he did not initiate any new therapy while he underwent screening for a potential clinical trial. His PSA then began to decline, to 1.9 ng/mL at 95 days and subsequently to 0.56 ng/mL, 126 days following AAW. His PSA has remained stable, between 0.4-0.5 ng/mL for 8 months now, without other evidence for disease progression.

Case 3

A 73-year-old man was diagnosed with Gleason 3+3=6 prostatic adenocarcinoma and metastatic lymph node and bone involvement. He initially underwent treatment with single-agent bicalutamide 50 mg daily, per patient request to minimize side effects, with a resultant PSA decline from 76.5 to 4.7 ng/mL, five months later.

Seven months after initiating bicalutamide, his PSA began to rise and therapy with leuprolide was initiated. His PSA climbed to 35 ng/mL five months after the addition of leuprolide. At that time, bicalutamide was withdrawn, yet his PSA rose to 61.1 ng/mL, 59 days after AAW (Figure 1C). While undergoing screening for a clinical trial, his PSA surprisingly dropped to 18.48 ng/mL, 84 days following AAW. His PSA did not rise again until it went up to 31.85 ng/mL, 256 days after AAW.

Discussion

While typically an AAW response to bicalutamide occurs within 6 weeks, here we describe a surprising and unexpected delayed PSA decline in 3 patients. Previous descriptions of the AAW response have not emphasized that PSA may continue to rise beyond the typical 4 to 6 week “washout” period before observing a PSA decline. These impressive PSA rises followed by delayed time until decline is not explained by the pharmacokinetics of bicalutamide and PSA.

This leads to review of potential biologic mechanisms for the AAW response. AR somatic mutations with clinical implications have been identified in approximately 10% of patients with mCRPC^{23, 24}. In particular, an *in-vitro* study using LNCaP-FGC cells documented development of a W741 androgen receptor mutation that allowed prostate cancer cells to use bicalutamide as an agonist²⁵. Progression to mCRPC may also be associated with AR amplification in approximately one-third of tumors²⁶. Using a LNCaP model, in situations with increased AR expression, AR antagonists, such as bicalutamide, have resulted in weak agonistic activity²⁷. Intriguingly, increased AR expression was associated with reduced or absent corepressor recruitment after bicalutamide treatment, and also was associated with alterations in recruitment of coactivators to the promoters of AR target genes. Therefore, amplification of AR in response to a low-level ligand environment may lead to alteration of the normal response to antiandrogens, and this may serve as an additional mechanism to explain the AAW response²⁸. Further investigation, with molecular evaluation of metastatic tumors, will be necessary to elucidate the biologic mechanism surrounding this phenomenon of delayed AAW response.

Conclusion

This case series should bring attention to the possibility that patients with PSA declines to the next therapy, after an unsuccessful 6-week long AAW, may yet still be related to a delayed AAW response and not the subsequent agent. We only noted this phenomenon because all 3 patients were in the process of screening (out of a total of 13 patients screened) for a clinical trial that required the entire 6-week washout period be complete, with continued rise in PSA, before extensive study-related procedures could occur. By the time the patients were ready to start the trial agent, more than 6 weeks had elapsed from the point of AAW, and we were surprised with dramatic PSA declines. Under normal circumstances, we would have already started the next line of therapy and the ensuing PSA decline would have been attributed to the subsequent therapeutic agent. We believe this is an unrecognized phenomenon that may lead to false attribution of response in both clinical trials and in standard practice, therefore further exploration to determine the frequency of this occurrence and a biologic explanation are required.

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Clinical Practice Points

- The antiandrogen withdrawal (AAW) syndrome is an important first therapeutic maneuver for patients on an oral antiandrogen in combination with luteinizing hormone releasing hormone therapy after progression of prostate cancer to a castration-resistant state.
- The clinical response, either a PSA decline or improvement in symptoms, occurs between 1-6 weeks, depending on the half-life of the oral antiandrogen.
- In this series, we report on 3 patients who had continued PSA rise 6 weeks after AAW followed by an unexpected delay until PSA decline, occurring later while waiting for clinical trial enrollment.
- Clinicians should be aware that after an unsuccessful 6-week AAW period, a subsequent PSA decline on the next line of therapy could result from a successful, yet delayed AAW response rather than the subsequent therapy.

Figure 1.

A-C. Sequential PSA measurements around the development of castration-resistance. The arrow indicates time of bicalutamide withdrawal. Time point 0 indicates the PSA value prior to withdrawal of bicalutamide.