CANCER DIAGNOSIS & PROGNOSIS
4: 684-688 (2024) doi: 10.21873/cdp.10382

Review

Androgen Receptor Signaling Inhibitor Withdrawal Syndrome After Castration-resistant Prostate Cancer

HIROSHI MASUDA

Department of Urology and Prostate Disease Center, Chiba Rosai Hospital, Chiba, Japan

Abstract. *Androgen-deprivation therapy is an extremely effective treatment for progressive prostate cancer. Previously, the first-line treatment for progressive prostate cancer was combined androgen blockade (CAB). If the disease progressed to castration-resistant prostate cancer, the administration of androgen receptor signaling inhibitors (ARSIs) was recommended. When elevated serum prostate-specific antigen (PSA) levels are seen during CAB treatment, it is important to suspect antiandrogen withdrawal syndrome (AWS), discontinue CAB, and monitor the changes in the serum PSA levels. If a reduction in the patient's PSA levels is subsequently observed, antiandrogens should be discontinued and the patient should be followed, but if their PSA level rises they should be transitioned to ARSI treatment. Recently, there have been reports of withdrawal syndrome (WS) after ARSI treatment. With the increased use of ARSIs, such as abiraterone acetate, enzalutamide, apalutamide, and dalorutamide, it is necessary to consider ARSI WS when a patient's serum PSA level increases during ARSI treatment. Unnecessary treatment can be avoided if the confirmation of ARSI WS is prioritized. Conversely, if it is not confirmed there is a risk that second-line treatment will be delayed. This is a review of recent studies of ARSI WS. It also discusses future prospects in this field.*

Correspondence to: Hiroshi Masuda, MD, Ph.D., Department of Urology, Chiba Rosai Hospital, 2-16 Tatsumidaihigashi, Ichihara, Chiba, 299-0003, Japan. Tel: +81 436741111, Fax: +81 436741151, e-mail: hrsmasuda@yahoo.co.jp

Key Words: Androgen-deprivation therapy, combined androgen blockade, androgen receptor signaling inhibitor, castration-resistant prostate cancer, prostate-specific antigen, review.

Androgen-deprivation therapy (ADT) has become the standard treatment for recurrent or advanced prostate cancer (PCa). Furthermore, first-generation antiandrogens, such as bicalutamide, flutamide, and chlormadinone acetate, are used in combination with castration, which is called "combined androgen blockade (CAB)". Labrie *et al*. reported that CAB sufficiently suppressed androgens derived from the testes and adrenal glands (1). In a comparative study performed in Japan, it was reported that the overall survival of patients with PCa treated with CAB involving bicalutamide was significantly longer than that of patients treated with castration alone (2-4). In addition, Matsuoka *et al*. reported in an overall analysis of metastatic PCa that although CAB did not significantly prolong overall survival or cancer-specific survival compared with castration alone, there was a significant prolongation of overall survival in the high-risk group with Japan Cancer of the Prostate Risk Assessment scores of ≥10 (5). It is widely known that CAB is used more frequently in Japan than in Western countries, and CAB therapy has been performed as a first-line hormonal therapy for metastatic PCa in Japan. However, in recent years the standard treatment for metastatic PCa has included the combined use of CAB with docetaxel or androgen receptor signaling inhibitors (ARSIs). Even in the era of availability of ARSIs, CAB is a treatment option suitable for selected patients with metastatic hormone-sensitive prostate cancer (HSPC). Furthermore, CAB may be economically beneficial (6).

Kelly *et al*. reported that in cases in which patients exhibited elevated prostate-specific antigen (PSA) levels after CAB and conversion to castration-resistant prostate cancer (CRPC), the PSA level was reduced after the discontinuation of an antiandrogen (flutamide) (7). This is indicative of so-called antiandrogen withdrawal syndrome (AWS). AWS is defined as a decline in the patient's PSA level of >50% after the discontinuation of antiandrogenic therapy, in the context of CAB treatment. Suzuki *et al*. demonstrated that the incidence of AWS upon CAB treatment ranged from 12.8% to 15.5% in Japan (8). Moreover, they found no significant difference in the PSA level in response to treatment with a second-line, first-

generation antiandrogen between men who did and did not exhibit AWS after being treated with a first-line antiandrogen. In another study, it was found that approximately 15-30% of patients exhibited a PSA level reduction of >50% after the discontinuation of antiandrogens (9). The observed response rates, which were as high as 30%, may have been directly related to the duration of treatment with androgen receptor (AR) blockers (10). AWS is a specific phenomenon that is observed during the treatment of PCa. Prior to the advent of the new generation of hormonal therapies, AWS was used to justify delaying the start of docetaxel-based chemotherapy in patients who continued receiving ADT without bicalutamide, providing only serological progression was seen (11). If the patient's PSA level subsequently declines, antiandrogens are discontinued and the patient is followed, whereas if their PSA level increases the patient is switched to ARSI. Similar to the AWS seen in CAB, recently there have been several reports of withdrawal syndrome (WS) occurring after the discontinuation of ARSI treatment (12-14). Also, there is a trend toward the use of ARSIs as first-line treatments for metastatic HSPC, and there has been an increase in the frequency at which ARSIs are administered. It has been reported that abiraterone acetate WS was observed after the initiation of up-front therapy for high-risk PCa (15). Up-front therapy in combination with an ARSI is the first-line treatment for metastatic HSPC. If an elevated PSA level is observed during ARSI treatment, ARSI WS should be considered. Many authors have questioned whether WS occurs with these newer hormonal therapies, such as enzalutamide and abiraterone acetate. Based on recent studies, I review ARSI WS and discuss future prospects in this field.

Enzalutamide Withdrawal Syndrome (EWS)

Enzalutamide was the first second-generation antiandrogenic drug approved for use in the treatment of CRPC. There have been two retrospective studies of enzalutamide withdrawal syndrome (EWS), a phenomenon in which a reduction in PSA levels is observed after the discontinuation of enzalutamide (12, 13). In the first study, Rodriguez-Vida *et al*. investigated 30 patients with metastatic CRPC who were administered enzalutamide (12). Three patients showed reduced PSA levels after the discontinuation of enzalutamide. However, only one of these cases met the criteria for the classical definition of AWS (a >50% reduction in the PSA level). Regrettably, no predictors of the treatment response were identified. In another study, von Klot *et al*. reported that EWS was observed in 31 cases from six different centers in Germany (13). Although 31 cases of EWS were examined, there was no reduction in the PSA level in any of them. von Klot *et al*. concluded that, if it exists, EWS is very rare when enzalutamide is administered for metastatic CRPC after taxane-based chemotherapy and that it has no clinical impact in this setting. This was attributed to differences in the pharmacokinetics of enzalutamide, although it was suggested that further investigations should be performed in different settings. These retrospective analyses involved patients who had already been treated with docetaxel-based chemotherapy. There was also a case report of a patient who developed EWS 40 days after the discontinuation of enzalutamide (16). Mosca *et al*. suggested that EWS may occur in the early phase of CRPC (17). Recently, Poole *et al*. described PSA reductions occurring in five of 47 metastatic CRPC patients after the discontinuation of enzalutamide (18). They concluded that the frequency of EWS was low and that the condition had a short duration. Moreover, they suggested that the occurrence of WS after enzalutamide treatment was not clinically meaningful. Therefore, it may not be necessary to consider this phenomenon in clinical practice. Poole *et al*. also conducted the largest study from a single institution (19). The latter study showed PSA reductions in five of 72 (7%) patients with metastatic CRPC after the discontinuation of enzalutamide. Only one case met the definition for WS. However, the median EWS response time (until subsequent PSA progression) was six weeks, which was very short. The mechanism underlying EWS has not been fully investigated. Poole *et al*. concluded that EWS is not very common; has a short duration; and cannot be predicted using patient, disease, or treatment-related characteristics.

Abiraterone Acetate Withdrawal Syndrome (AbAWS)

Abiraterone acetate (AbA) is an androgen synthesis inhibitor, which has been approved for use in the treatment of CRPC, in both the pre- and post-docetaxel settings (20, 21). In 2012, Gauthier *et al*. first reported AbAWS in patients with metastatic CRPC (14). In the latter study, they reported that the patients' PSA levels continued to decline for at least three months after the discontinuation of AbA. Witjes *et al*. have also described the same response (22). Caffo *et al*. demonstrated that three of 19 patients in whom AbA was discontinued due to disease progression exhibited PSA level reductions of >50%. In the two patients who were observed long-term, positron emission tomography scans performed three months after the discontinuation of AbA showed a significant reduction in uptake (SUVmax) values (23). Another study retrospectively evaluated 66 of 218 patients in whom AbA was discontinued owing to disease progression (24). Of the 66 patients, 21 (32%) had reduced PSA levels, and there were four patients (6%) whose PSA levels were reduced by >50%. For the other patients, new treatment was started immediately after the discontinuation of AbA.

Regarding predictors of ARSI WS, a retrospective study examining predictors of AbAWS in 70 patients with CRPC was reported (25). Among the 70 patients in whom AbA was discontinued due to elevated PSA levels, 11 experienced

Table I. *Retrospective studies of androgen receptor signaling inhibitor (ARSI) withdrawal syndrome.*

Drug	Patients (N)	Withdrawal syndrome (N)	Frequency (%)	Half-life	Authors (Ref)
Enzalutamide	31	0	0	4.7~8.4 days	Von Klot *et al.* (13)
	30	3	10		Rodriguez-Vida *et al.* (12)
	72	5	7		Poole *et al.* (18)
	47	5	11		Poole *et al.* (19)
Abiraterone acetate	19	3	16	16.6 h	Caffo *et al.* (23)
	70	11	16		Almendros *et al.* (25)
	66	4	6		Albiges *et al.* (24)
Apalutamide	No reports			5.4 days	

AbAWS. The median duration of observation after AbAWS was 8.2 months. A PSA level of 30 ng/ml or higher at the time of AbA induction, an ISUP Gleason grade of group 4 or higher, and the presence of stage 4 disease at diagnosis were considered to be predictors of AbAWS. In the latter study, it was stated that the frequency of AbAWS is not negligible and that AbAWS results in an extended response after the discontinuation of AbA, which results in prolonged overall survival. These results may provide a new option for the treatment of metastatic CRPC. Suzuki *et al.* reported that although the presence/absence of AWS was not a predictor of the outcomes of secondary hormone therapy, it was a prognostic factor for advanced PCa (8). In the southwest oncology group prospective study, predictors of the development of AWS were more common in patients who had been using antiandrogenic agents for longer (26). While the pathophysiological mechanisms underlying AbAWS are not fully understood, several hypotheses have been proposed. It is possible that a mutant AR is activated by an alternative ligand and that the ligand-binding domain contributes to AbAWS (9, 27). Regarding the mechanism of AbAWS development, there is speculation that the discontinuation of AbA reduces serum progesterone levels and activates mutant AR, resulting in the development of AbAWS. It is speculated that the discontinuation of AbA causes the downregulation of multiple sites of the AR signaling pathway, resulting in the development of AbAWS (15). AbA is usually administered in combination with prednisone to avoid hypocortisolemia and the consequent elevated adrenocorticotropic hormone levels (28). The glucocorticoid receptor (GR) gene is one of the most upregulated genes in antiandrogen-resistant PCa and shares many target genes with AR (29). Therefore, prednisone may bypass AR blockade and dihydrotestosterone deficiency through the GR. When the PSA level rises after the administration of AbA, both AbA and prednisolone are stopped simultaneously. Prednisolone is known to act as a specific alternative ligand for certain mutant ARs (9). AbAWS may be partly influenced by prednisolone discontinuation rather than AbA discontinuation. However, it has been reported that AbAWS has been documented even in patients who continued receiving steroids after the discontinuation of AbA (30). Marin *et al.* reported that it was possible to confirm long-term AbAWS and delay docetaxel treatment for eight months without discontinuing prednisolone (31). They noted that prednisone was not associated with AbAWS, although the details were not reported. In addition, Kato *et al.* reported that the frequency of AbAWS did not correlate with prednisolone use and that AbAWS was mainly associated with AbA discontinuation (27). According to a recent case report, even spironolactone withdrawal was associated with a dramatic response in a patient with metastatic CRPC (32). Therefore, it is recommended that when PSA values are elevated after AbA administration, AbA alone should be discontinued, and prednisolone should be continued.

In recent years, it has become possible to administer AbA as a first-line treatment for metastatic HSPC. Tani *et al.* reported a case in which AbAWS occurred after the administration of AbA for the first time (15). After the discontinuation of AbA, the patient's PSA levels decreased and were maintained at low levels for five months. They stated that if patients with metastatic HSPC who were treated with up-front AbA were found to have elevated PSA levels, they should not be immediately moved to the next treatment. Moreover, they said that if the patient's condition permitted it was clinically acceptable to discontinue AbA for approximately one month and follow the patient's PSA levels.

In the future, it is anticipated that the use of AbA as an initial treatment may increase, and hence, the opportunity to evaluate AbAWS may also increase. It would be extremely useful if it were possible to predict AbAWS prior to its occurrence. It may be concluded that AbAWS is not a rare clinical phenomenon, and it may be possible to evaluate its clinical impact better in the near future. When PSA levels rise during the administration of AbA, it is acceptable to stop the AbA treatment and wait until after the patient's PSA levels have been verified before moving on to the next stage of treatment.

Apalutamide Withdrawal Syndrome (ApWS)

Although it has been reported that the discontinuation of apalutamide should be considered when severe dermatological symptoms occur (33), WS has not been reported after the discontinuation of apalutamide. Apalutamide has almost the same chemical formulation as enzalutamide, but it causes different adverse events. While there have not been any previous reports of ApWS, considering the rarity of EWS, it is highly possible that ApWS will not be observed in the future. Apalutamide has a relatively long half-life, similar to enzalutamide. Therefore, when patients treated with apalutamide exhibit elevated PSA levels, it is necessary to consider switching them to other ARSIs after a period of time (Table I).

Dalorutamide (DaWS)

Similar to apalutamide, WS has not been reported after the discontinuation of dalorutamide.

Future Perspectives

It was found that there are different predictors of AWS for antiandrogens and ARSIs. However, it is necessary to accumulate further data to gain a full understanding of the predictors of WS. To summarize the findings of previous studies, if patients with advanced PCa are treated with first-generation antiandrogens and develop CRPC, WS should be considered. It was thought that if a patient was initially treated with ARSIs, ARSI WS was unlikely to occur, and it would be better to transition to second-line treatment. While it is important to be ready to consider WS in patients treated with ARSIs, clinicians should always pay careful attention to patients' medical conditions and the state of their cancer, and provide appropriate treatment.

Therefore, how long should ARSIs be discontinued to confirm that a patient is experiencing ARSI WS? Although it has been reported that the optimal withdrawal period for AbA discontinuation is one month, (15) as the half-lives of enzalutamide and apalutamide are long and equivalent to the half-life of bicalutamide, it would seem that two months would be an appropriate discontinuation period for these drugs.

Conclusion

In conclusion, it seems that second-generation antiandrogens cause WS less frequently, and such WS is of less clinical significance than that caused by first-generation antiandrogens. Therefore, there may be a temptation to ignore such WS. However, in some cases it may have a clinically relevant impact, and hence, should not be completely ignored.

In this review article, we have omitted molecular pathophysiological studies and focused on real-world clinical practice when reviewing the literature. This review may be of use in daily clinical practice.

Conflicts of Interest

The Author has no conflicts of interest in relation to this study.

Funding

This research received no external funding.

References

1 Labrie F, Dupont A, Belanger A, Cusan L, Lacourciere Y, Monfette G, Laberge JG, Emond JP, Fazekas AT, Raynaud JP, Husson JM: New hormonal therapy in prostatic carcinoma: combined treatment with an LHRH agonist and an antiandrogen. Clin Invest Med 5(4): 267-275, 1982.

2 Akaza H, Hinotsu S, Usami M, Arai Y, Kanetake H, Naito S, Hirao Y, Study Group for the Combined Androgen Blockade Therapy of Prostate Cancer: Combined androgen blockade with bicalutamide for advanced prostate cancer. Cancer 115(15): 3437-3445, 2009. DOI: 10.1002/cncr.24395

3 Akaza H, Miyanaga N, Takashima N, Naito S, Hirao Y, Tsukamoto T, Fujioka T, Mori M, Kim WJ, Song JM, Pantuck AJ: Comparisons of percent equol producers between prostate cancer patients and controls: Case-controlled studies of isoflavones in Japanese, Korean and American residents. Jpn J Clin Oncol 34(2): 86-89, 2004. DOI: 10.1093/jjco/hyh015

4 Arai Y, Akaza H, Deguchi T, Fujisawa M, Hayashi M, Hirao Y, Kanetake H, Naito S, Namiki M, Tachibana M, Usami M, Ohashi Y: Evaluation of quality of life in patients with previously untreated advanced prostate cancer receiving maximum androgen blockade therapy or LHRHa monotherapy: a multicenter, randomized, double-blind, comparative study. J Cancer Res Clin Oncol 134(12): 1385-1396, 2008. DOI: 10.1007/s00432-008-0409-z

5 Matsuoka T, Kawai K, Kimura T, Kojima T, Onozawa M, Miyazaki J, Nishiyama H, Hinotsu S, Akaza H: Long-term outcomes of combined androgen blockade therapy in stage IV prostate cancer. J Cancer Res Clin Oncol 141(4): 759-765, 2015. DOI: 10.1007/s00432-014-1856-3

6 Miyazawa Y, Sekine Y, Arai S, Oka D, Nakayama H, Syuto T, Nomura M, Koike H, Matsui H, Shibata Y, Suzuki K: Prognostic factors in hormone-sensitive prostate cancer patients treated with combined androgen blockade: a consecutive 15-year study at a single Japanese institute. In Vivo 35(1): 373-384, 2021. DOI: 10.21873/invivo.12268

7 Kelly WK, Scher HI: Prostate specific antigen decline after antiandrogen withdrawal: the flutamide withdrawal syndrome. J Urol 149(3): 607-609, 1993. DOI: 10.1016/s0022-5347(17)36163-3

8 Suzuki H, Okihara K, Miyake H, Fujisawa M, Miyoshi S, Matsumoto T, Fujii M, Takihana Y, Usui T, Matsuda T, Ozono S, Kumon H, Ichikawa T, Miki T, Nonsteroidal Antiandrogen Sequential Alternation for Prostate Cancer Study Group: Alternative nonsteroidal antiandrogen therapy for advanced prostate cancer that relapsed after initial maximum androgen blockade. J Urol 180(3): 921-927, 2008. DOI: 10.1016/j.juro.2008.05.045

9 Lorente D, Mateo J, Zafeiriou Z, Smith AD, Sandhu S, Ferraldeschi R, de Bono JS: Switching and withdrawing

hormonal agents for castration-resistant prostate cancer. Nat Rev Urol 12(1): 37-47, 2015. DOI: 10.1038/nrurol.2014.345
10 Paul R, Breul J: Antiandrogen withdrawal syndrome associated with prostate cancer therapies. Drug Safety 23(5): 381-390, 2000. DOI: 10.2165/00002018-200023050-00003
11 Leone G, Tucci M, Buttigliero C, Zichi C, Pignataro D, Bironzo P, Vignani F, Scagliotti GV, Di Maio M: Antiandrogen withdrawal syndrome (AAWS) in the treatment of patients with prostate cancer. Endocr Relat Cancer 25(1): R1-R9, 2018. DOI: 10.1530/ERC-17-0355
12 Rodriguez-Vida A, Bianchini D, Van Hemelrijck M, Hughes S, Malik Z, Powles T, Bahl A, Rudman S, Payne H, de Bono J, Chowdhury S: Is there an antiandrogen withdrawal syndrome with enzalutamide? BJU Int 115(3): 373-380, 2015. DOI: 10.1111/bju.12826
13 von Klot CA, Kramer MW, Böker A, Herrmann TR, Peters I, Kuczyk MA, Ligges U, Gschwend JE, Retz M, Schmid SC, Stenzl A, Schwentner C, Todenhöfer T, Stöckle M, Ohlmann CH, Azone I, Mager R, Bartsch G, Haferkamp A, Heidenreich A, Piper C, Merseburger AS: Is there an anti-androgen withdrawal syndrome for enzalutamide? World J Urol 32(5): 1171-1176, 2014. DOI: 10.1007/s00345-014-1288-3
14 Gauthier H, Bousquet G, Pouessel D, Culine S: Abiraterone acetate withdrawal syndrome: does it exist? Case Rep Oncol 5(2): 385-387, 2012. DOI: 10.1159/000341564
15 Tani M, Hayashi Y, Miki A, Wakita T, Horibe Y, Kakuta Y, Tsutahara K, Takao T: A case of abiraterone acetate withdrawal syndrome after initiation of upfront abiraterone therapy for high-risk prostate cancer. IJU Case Rep 6(5): 282-285, 2023. DOI: 10.1002/iju5.12604
16 Phillips R: Prostate cancer: an enzalutamide antiandrogen withdrawal syndrome. Nat Rev Urol 11(7): 366-366, 2014. DOI: 10.1038/nrurol.2014.145
17 Mosca A: Enzalutamide withdrawal syndrome: is there a rationale? BJU International 115(3): 348-349, 2015. DOI: 10.1111/bju.12908
18 Poole A, Gill D, Hahn AW, Johnson E, Carroll E, Boucher K, Nussenzveig R, Maughan B, Agarwal N: Incidence and characterization of antiandrogen withdrawal syndrome after discontinuation of treatment with enzalutamide in castration-resistant prostate cancer. Clin Genitourin Cancer 16(1): e169-e172, 2018. DOI: 10.1016/j.clgc.2017.08.017
19 Poole A, Gill DM, Hahn AW, Johnson E, Carroll E, Batten JA, Gupta S, Boucher KM, Maughan BL, Agarwal N: Incidence and characterization of antiandrogen withdrawal syndrome (AAWS) after enzalutamide (ENZA) in patients (pts) with metastatic castration-refractory prostate cancer (mCRPC). J Clin Oncol 35(6_suppl): 228-228, 2017. DOI: 10.1200/JCO.2017.35.6_suppl.228
20 Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, Fizazi K, Mainwaring P, Piulats JM, Ng S, Carles J, Mulders PF, Basch E, Small EJ, Saad F, Schrijvers D, Van Poppel H, Mukherjee SD, Suttmann H, Gerritsen WR, Flaig TW, George DJ, Yu EY, Efstathiou E, Pantuck A, Winquist E, Higano CS, Taplin ME, Park Y, Kheoh T, Griffin T, Scher HI, Rathkopf DE, COU-AA-302 Investigators: Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 368(2): 138-148, 2013. DOI: 10.1056/NEJMoa1209096
21 de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, Chi KN, Jones RJ, Goodman OB Jr, Saad F, Staffurth JN, Mainwaring P, Harland S, Flaig TW, Hutson TE, Cheng T, Patterson H, Hainsworth JD, Ryan CJ, Sternberg CN, Ellard SL, Fléchon A, Saleh M, Scholz M, Efstathiou E, Zivi A, Bianchini D, Loriot Y, Chieffo N, Kheoh T, Haqq CM, Scher HI, COU-AA-301 Investigators: Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 364(21): 1995-2005, 2011. DOI: 10.1056/NEJMoa1014618
22 Witjes JA: A case of abiraterone acetate withdrawal. Eur Urol 64(3): 517-518, 2013. DOI: 10.1016/j.eururo.2013.06.013
23 Caffo O, Palermo A, Veccia A, Maines F, Chierichetti F, Berruti A, Galligioni E: Biochemical and objective response to abiraterone acetate withdrawal: incidence and clinical relevance of a new scenario for castration-resistant prostate cancer. Urology 82(5): 1090-1093, 2013. DOI: 10.1016/j.urology.2013.07.029
24 Albiges L, Auclin E, Rousseau B, Boughalem E, Levy A, Loriot Y, Di Palma M, Massard C, Fizazi K: Is there a withdrawal syndrome with abiraterone acetate (AA)? J Clin Oncol 31(6): 89, 2013. DOI: 10.1200/jco.2013.31.6_suppl.89
25 Almendros S, Berenguer-Francés MA, Ferrer-González F, Boladeras A, Guix I, Guedea F: Predictive factors for abiraterone withdrawal syndrome. Actas Urol Esp (Engl Ed) 43(6): 300-304, 2019. DOI: 10.1016/j.acuro.2019.01.003
26 Sartor AO, Tangen CM, Hussain MH, Eisenberger MA, Parab M, Fontana JA, Chapman RA, Mills GM, Raghavan D, Crawford ED, Southwest Oncology Group: Antiandrogen withdrawal in castrate-refractory prostate cancer: a Southwest Oncology Group trial (SWOG 9426). Cancer 112(11): 2393-2400, 2008. DOI: 10.1002/cncr.23473
27 Kato T, Komiya A, Yuasa J, Kaga K, Kaga M, Kojima S, Naya Y, Isaka S: Abiraterone acetate withdrawal syndrome: Speculations on the underlying mechanisms. Oncol Lett 15(2): 2669-2672, 2018. DOI: 10.3892/ol.2017.7628
28 Auchus RJ, Yu MK, Nguyen S, Mundle SD: Use of prednisone with abiraterone acetate in metastatic castration-resistant prostate cancer. Oncologist 19(12): 1231-1240, 2014. DOI: 10.1634/theoncologist.2014-0167
29 Arora VK, Schenkein E, Murali R, Subudhi SK, Wongvipat J, Balbas MD, Shah N, Cai L, Efstathiou E, Logothetis C, Zheng D, Sawyers CL: Glucocorticoid receptor confers resistance to antiandrogens by bypassing androgen receptor blockade. Cell 155(6): 1309-1322, 2013. DOI: 10.1016/j.cell.2013.11.012
30 Azad AA, Eigl BJ: Evaluation of prostate-specific antigen response following cessation of abiraterone acetate: is there evidence for a withdrawal syndrome? Eur Urol 65(2): 504-505, 2014. DOI: 10.1016/j.eururo.2013.10.035
31 Marin S, Querol R, Campins L, Miarons M, Font A, Lianes P: Long-term abiraterone withdrawal syndrome. J Clin Pharm Ther 43(5): 714-716, 2018. DOI: 10.1111/jcpt.12693
32 Flynn T, Guancial EA, Kilari M, Kilari D: Case report: Spironolactone withdrawal associated with a dramatic response in a patient with metastatic castrate-resistant prostate cancer. Clin Genitourin Cancer 15(1): e95-e97, 2017. DOI: 10.1016/j.clgc.2016.08.006
33 Wang Q, Cao H, Zhang X, Wu H, Tang Z: Case report: Apalutamide-induced severe lethal cutaneous adverse effects in China. Front Immunol 14: 1291564, 2024. DOI: 10.3389/fimmu.2023.1291564

Received August 18, 2024
Revised September 11, 2024
Accepted September 12, 2024