

PSA response following the ‘steroid switch’ in patients with castration-resistant prostate cancer treated with abiraterone: A case report

TOMONORI KATO¹, SATOKO KOJIMA¹, AYUMI FUJIMOTO¹, KOTARO OTSUKA¹,
TAKAHITO SUYAMA¹, KYOKUSHIN HOU¹, KAZUHIRO ARAKI¹, HIROSHI MASUDA¹,
KAZUTO YAMAZAKI², AKIRA KOMIYA³ and YUKIO NAYA¹

Departments of ¹Urology and ²Pathology, Teikyo University Chiba Medical Center, Ichihara, Chiba 299-0111;

³Department of Urology, Chiba University Graduate School of Medicine, Chiba, Chiba 260-8677, Japan

Received December 30, 2017; Accepted August 7, 2018

DOI: 10.3892/ol.2018.9321

Abstract. A 69-year-old man presented initially with back pain and incomplete bilateral lower limb paralysis. The level of prostate-specific antigen (PSA) in the patient was elevated to 167.0 ng/ml, and multiple bone metastases were detected. Thoracic laminectomy was performed in an emergency due to spinal decompression. Subsequently, the patient was diagnosed with prostate cancer from an examination of resected bone specimens. Combined androgen blockade with degarelix and bicalutamide was initiated in October 2013. Consequently, the serum PSA level decreased to <1.0 ng/ml, but thereafter gradually increased. Subsequent bicalutamide withdrawal response was not observed, and switch of anti-androgen therapy to flutamide also resulted in a poor response. Then, abiraterone (1,000 mg daily) in combination with prednisolone (10 mg daily) was initiated when the level of PSA increased to 35.9 ng/ml in June 2015. The level of PSA decreased to the lowest point of 4 ng/ml; however, PSA level increased again to 21.7 ng/ml in April 2016. Consequently, a ‘steroid switch’ was attempted. Abiraterone therapy was continued, but concomitant corticosteroid was switched from prednisone to dexamethasone (1.0 mg per day). Fortunately, serum PSA level decreased promptly to the lowest point of 0.6 ng/ml. In the present case report, a review of recent literature was presented

and potential explanations of the mechanism underlying the ‘steroid switch’ were described. Pharmacokinetic differences between dexamethasone and prednisolone may partially explain why the ‘steroid switch’ occurs. Other mechanisms may include the activation of the glucocorticoid receptor, mineralocorticoid receptor and/or mutant androgen receptor. Corticosteroids accelerate a number of transcription factors, cellular growth factors and cytokines, which may also be potential mechanisms. The ‘steroid switch’ at PSA progression might be a feasible option for therapy, which may delay the development of the disease. Although the underlying mechanisms require further study, clinicians should pay attention to this phenomenon.

Introduction

Abiraterone is a potent CYP17 inhibitor that blocks androgen synthesis and improves survival in castration-resistant prostate cancer (CRPC), which is generally administered in association with a daily dose of 10 mg prednisolone to prevent mineralocorticoid excess (1). Recent novel therapies for metastatic CRPC (mCRPC), including abiraterone and taxane-based chemotherapy, require concomitant corticosteroids (1,2). Recent studies have suggested a survival advantage with the addition of cytotoxic docetaxel chemotherapy with prednisolone for newly diagnosed patients with high-volume metastatic disease (3). More recently, abiraterone acetate plus prednisone in addition to initial androgen-deprivation therapy also demonstrated increased overall survival in men with newly diagnosed metastatic prostate cancer (4). Currently, corticosteroids are also frequently used in palliative care (5). Therefore, corticosteroids are more frequently used for prolonged periods than previously for treating mCRPC.

Previously, it had been assumed that antitumor effects of corticosteroids are caused by reduced synthesis of adrenal androgens due to suppression of pituitary adrenocorticotrophic hormone (ACTH) production (6,7). Accordingly, any corticosteroids, including prednisolone, hydrocortisone and dexamethasone, were all thought to be equally effective (6). However, current clinical trials suggested that dexamethasone

Correspondence to: Dr Tomonori Kato, Department of Urology, Teikyo University Chiba Medical Center, 3426-3 Anesaki, Ichihara, Chiba 299-0111, Japan
E-mail: jpn3899kato@yahoo.co.jp

Abbreviations: PSA, prostate specific antigen; ACTH, adrenocorticotrophic hormone; CRPC, castration-resistant prostate cancer; mCRPC, metastatic castration resistant prostate cancer; AR, androgen receptor; GR, glucocorticoid receptor; MR, mineralocorticoid receptor; IL, interleukin

Key words: metastatic castration-resistant prostate cancer, abiraterone, prednisolone, dexamethasone, steroid switch

would be more potent compared with prednisolone for treating mCRPC for monotherapy and combination therapy (8,9). In addition, a ‘steroid switch’, that is, switching concomitant corticosteroids from prednisone to dexamethasone, is known to have antitumoral effects on patients with mCRPC (10,11).

In this manuscript, a patient with mCRPC is reported. The patient had a drastic decrease in the level of prostate-specific antigen (PSA) following a ‘steroid switch’ during abiraterone treatment. A review of the recent literature is provided, and potential explanations of the mechanism underlying this phenomenon are described.

Case report

A 69-year-old man presented initially with back pain and incomplete paralysis of the bilateral lower extremities. The level of PSA in the patient elevated to 167.0 ng/ml. Further evaluation revealed multiple bone metastases involving thoracic spinal compression. Thoracic laminectomy was immediately performed for spinal decompression. The resected lesion was pathologically consistent with metastatic adenocarcinoma of the prostate (Fig. 1). The patient was diagnosed with prostate cancer T3bN0M1b (Fig. 2).

Combined androgen blockade with degarelix and bicalutamide was started in October 2013. Monthly infusions of zoledronic acid were simultaneously initiated. The kinetics of PSA during treatment is displayed in Fig. 3. The serum level of PSA decreased to <1.0 ng/ml, however thereafter gradually increased. Subsequent anti-androgen withdrawal response was not observed following the discontinuation of bicalutamide. Then, anti-androgen switch to flutamide was attempted, which also resulted in a poor response.

Consequently, abiraterone was initiated at a standard dose of 1,000 mg daily in combination with 10 mg prednisolone when the level of PSA increased to 35.9 ng/ml in June 2015. Immediately, the level of PSA decreased to the lowest point of 4.0 ng/ml. However, after a while, the level of PSA gradually increased again to 21.7 ng/ml in April 2016.

The patient had limited treatment options at that time; he was considered to be unfit for chemotherapy because he had developed severe bisphosphonate-related osteonecrosis of the jaw. Considering the scarcity of the available treatment options, a ‘steroid switch’ was attempted prior to starting further therapy. The ‘steroid switch’ involved a continuation of abiraterone therapy, but concomitant steroid was switched from prednisone to dexamethasone (1.0 mg per day), which may have effects on the values of PSA (10,11). Fortunately, a good PSA response was observed, and the serum PSA level promptly decreased to 0.6 ng/ml. The levels of PSA following the ‘steroid switch’ are displayed in Fig. 3.

As the level of PSA decreased and became stable following the ‘steroid switch’ it was decided to continue with dexamethasone monotherapy and discontinue abiraterone. It was hypothesized that dexamethasone itself might be effective, so abiraterone is no longer necessary. However, following the deletion of abiraterone, the serum level of PSA had slowly started to increase again, and local radiological progression was hypothesized. Subsequently, the patient received 72 Gy of external beam radiation onto the prostate gland, which exhibited a temporary response. However the level of increased again after a while. Re-exposure with

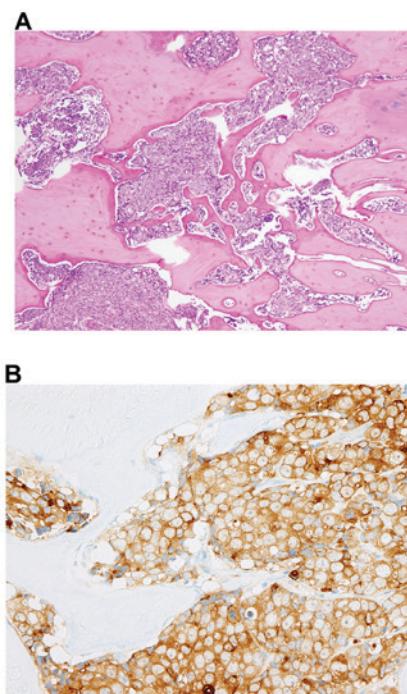


Figure 1. Identification of metastatic tumor cells by H&E staining and confirmation by IHC with PSA. Infiltration by tumor cells in bone marrow with adjacent bone trabeculae as indicated by sections from a bone marrow biopsy. (A) H&E staining. Magnification, x40. (B) IHC sections for PSA indicated diffuse positivity in tumor cells with adjacent bone trabeculae. Magnification, x200. PSA, prostate-specific antigen; H&E, hematoxylin and eosin; IHC, immunohistochemistry.

abiraterone was attempted when the serum PSA level increased to 13.4 ng/ml in June 2017. Temporally, the level of PSA once decreased again to 8.1 ng/ml in response to the re-exposure of abiraterone. However, the levels of PSA continued to increase thereafter.

In the present study, written informed consent was obtained from the patient for the publication of the present case report and any accompanying images. No ethics approval was obtained as this was a case report with no direct impact on patient outcome.

Discussion

Corticosteroids have been used in the treatment of CRPC for over three decades. Although it was used as a monotherapy, corticosteroids demonstrate substantial biochemical, clinical and radiologic responses (12,13). Corticosteroids are also used in combination with cytotoxic chemotherapy to palliate its toxicities, and with abiraterone to prevent mineralocorticoid excess (1,2). In addition, corticosteroids are also widely prescribed in palliative care to improve nonspecific symptoms, including pain, anorexia, nausea, weakness and general well-being (5). Therefore, patients with mCRPC are more frequently exposed to corticosteroid therapy than before.

As an antitumoral agent for CRPC, corticosteroids are generally used as low-dose, continuous and administered orally. A ‘low dose’ is usually considered to be prednisone or prednisolone at 5-15 mg/day and dexamethasone at 0.5-3 mg/day (14). On the other hand, intermittent relatively higher doses of corticosteroids in combination with

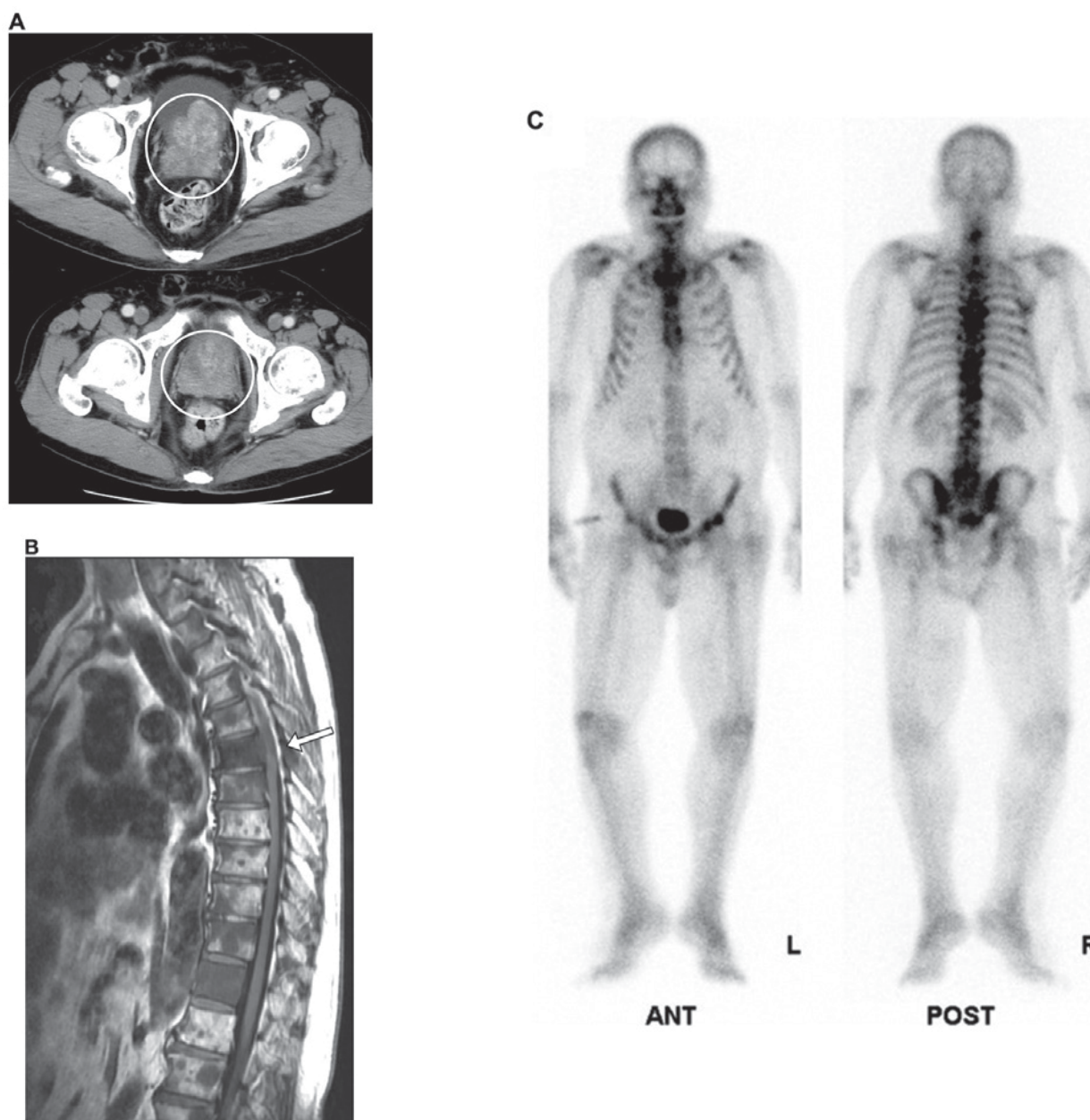


Figure 2. CT and MRI findings. The patient was diagnosed with prostate cancer T3bN0M1b. (A) CT indicated massive prostate tumor (circle) that invaded the bilateral seminal vesicle without marked lymph node metastases. (B) MRI of the spine revealed a metastatic tumor extending from Th5 with spinal cord compression (arrow). The patient was immediately treated by emergency Th5-6 laminectomy and epidural decompression. (C) Bone scintigraphy indicated multiple bone metastases in the vertebrae, ribs, pelvis, sternum and skull. CT, computed tomography; MRI, magnetic resonance imaging.

chemotherapy have demonstrated insufficient antitumor effects in CRPC (9,15).

Among corticosteroids, prednisolone is the most commonly used corticosteroid in combination with abiraterone or chemotherapy, and it is currently recommended by more than one guidelines including those from the AUA, EAU and NCCN (14). Corticosteroids are well known to suppress pituitary ACTH production, which leads to adrenal androgen suppression (7). Previously, the adrenal androgen suppression was assumed to be the main cause of the antitumor effect against CRPC. Accordingly, any corticosteroids including prednisolone, hydrocortisone and dexamethasone were once thought to be equally effective (6). However, current clinical trials suggested that dexamethasone could be more potent compared with prednisolone in the treatment of

mCRPC (8,9). Several non-randomized trials have suggested higher response rates with dexamethasone compared with prednisolone; the PSA response rate for CRPC was 27-38% for prednisolone (7.5-10 mg/day) and 40-62% for dexamethasone (0.5-1.5 mg/day) (8). Recent randomized phase 2 trial of dexamethasone 0.5 mg daily vs. prednisolone 10 mg daily as monotherapy for CRPC indicated improved PSA response rates for dexamethasone over prednisolone (9). PSA response rates and median time to PSA progression were 41 vs. 22% and 9.7 vs. 5.1 months for dexamethasone and prednisolone, respectively. However, this trend did not reach statistical significance (9).

Furthermore, a recent retrospective study examined patients with mCRPC who had undergone a 'steroid switch' from prednisolone to dexamethasone during abiraterone

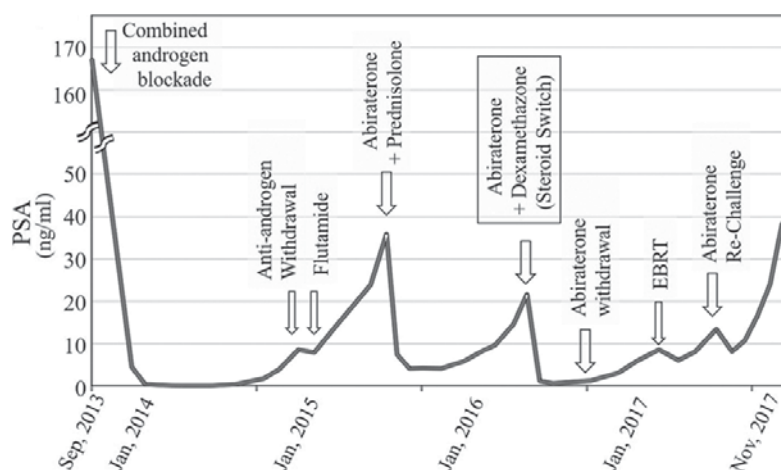


Figure 3. Time-course changes of serum PSA levels and therapeutic agents. Abiraterone was initiated in combination with prednisolone when PSA levels increased up to 35.9 ng/ml in June 2015. PSA reached the lowest level of 4.0 ng/ml; however, the level of PSA increased again to 21.7 ng/ml in April 2016. Consequently, a 'steroid switch' was attempted. Abiraterone therapy was continued, but concomitant corticosteroid was switched from prednisone to dexamethasone (1.0 mg per day). Consequently, serum PSA level decreased to the lowest point of 0.6 ng/ml. PSA, prostate-specific antigen.

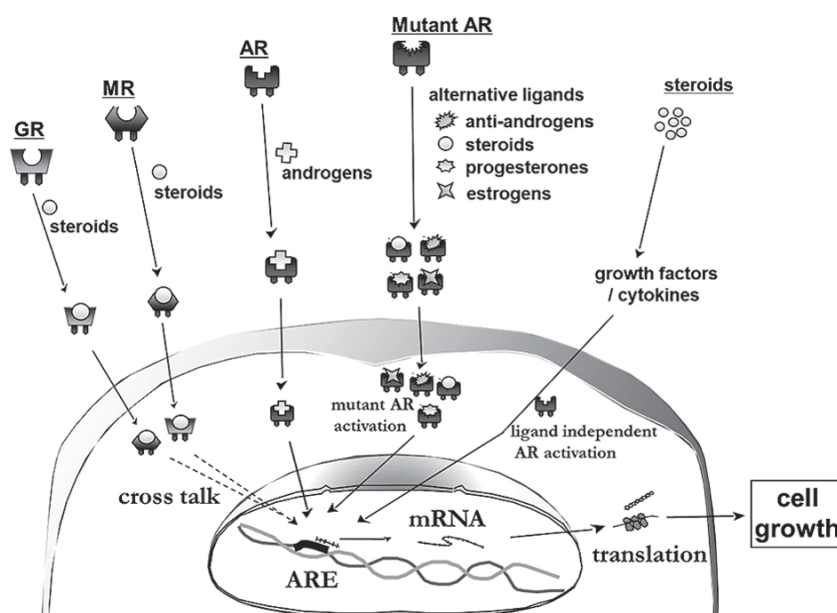


Figure 4. Suggested mechanisms of responses that are induced by the 'steroid switch': i) Activation of the GR and/or MR, ii) resistance occurs due to AR mutations and iii) responses derived from various cytokines and cellular growth factors, including IL-6, IL-8, HGF, TGF and VEGF. GR, glucocorticoid receptor; MR, mineralocorticoid receptor; HGF, hepatocyte growth factor; TGF, transforming growth factor; VEGF, vascular endothelial growth factor; IL, interleukin; AR, androgen receptor.

treatment. In this trial, 11 of 30 patients (39%) had confirmed decline ($\geq 30\%$) in PSA after the 'steroid switch' with a median time to PSA progression of 11.7 weeks (10). 'Steroid switch' is also able to occasionally induce a long-lasting biochemical response accompanied by a clinical and radiological improvement (10).

Potential mechanisms of responses induced by 'steroid switch' include: i) Pharmacokinetic differences between different corticosteroids, ii) activation of the glucocorticoid receptor (GR) and/or mineralocorticoid receptor (MR), iii) resistance occurs due to androgen receptor (AR) mutations and iv) responses derived from various cytokines and cellular growth factors, including interleukin (IL)6, IL8 and vascular endothelial growth factor (Fig. 4).

Pharmacokinetic differences between dexamethasone and prednisolone might explain the mechanisms. The half-life of dexamethasone is longer, which may produce a more effective suppression of ACTH and higher antitumoral activity than prednisolone (16). Dexamethasone is thought to be a more potent agent than prednisolone due to its stronger glucocorticoid activity and lower mineralocorticoid activity (17). A 10 mg of prednisolone recommended in the EAU guidelines, represents a higher glucocorticoid activity compared with commonly used low doses of dexamethasone (0.5-1.5 mg daily) (16).

Differences in the activation of the GR between dexamethasone and prednisolone might also be responsible for this phenomenon. GR expression was significantly

increased in patients with prostate cancer who were exposed to androgen deprivation (18). The AR and GR, which both are members of the nuclear steroid receptors, share common structures, mechanisms of action and several transcriptional targets (18,19). Cross-talk between AR and GR has been recently speculated. As a result of AR inhibition, AR signaling is bypassed via activated GR, which binds to nuclear androgen response elements and regulate AR target genes (18,19). As patients progress to CRPC, prednisolone is able to activate GR more, which may reverse with a 'steroid switch' to dexamethasone, which has a lower affinity for GR.

Although a limited number of studies have examined the role of MRs in CRPC, differences between dexamethasone and prednisolone in the activation of the MR may also cause alterations in efficacy (20). Resistances that occurs secondary to MR activation may be reversed with a 'steroid switch' to dexamethasone, which has a lower affinity for MR (17,20). MR is expressed in prostate cancer cells regardless of AR status and appears to be regulated by inflammatory cytokines, which are highly involved in the progression of prostate cancer (21). Subsequent changes in MR expression from inflammatory cytokines is also speculated to be involved in prostate cancer carcinogenesis (22).

It might also be possible that resistance occurs due to corticosteroid-responsive AR mutations that are activated by prednisolone but not by dexamethasone. AR mutations in the ligand-binding domain and/or hinge region are hypothesized to be responsible for stimulating effects of alternative ligands other than testosterone (23). AR mutations that are activated by corticosteroids, including prednisolone and dexamethasone, have been identified (24,25).

Glucocorticoids have an anti-angiogenic and anti-inflammatory effect on prostate cancer by modulating transcription factors, cellular growth factors and cytokines, which may also contribute to the differences in the antitumor activity (26,27). Dexamethasone has an anti-angiogenic effect on prostate cancer, which mediated by the activation of GR-mediated signaling, leading to a reduction in IL-6, IL-8 and vascular endothelial growth factor expression (28,29). IL-6 is known to stimulate the growth of prostate cancer cells through GRs in an androgen-independent manner and has been demonstrated to activate the AR through a STAT3-dependent pathway (17,30). In addition, changes in serum levels of IL-6 were significantly associated with the response to dexamethasone in patients with CRPC (8).

The exact starting point for turning to 'steroid switch' is not determined yet. 'Steroid switch' is generally performed at progression during abiraterone treatment (10,11). It is reasonable to consider switching concomitant steroids when the level of PSA increases during abiraterone treatment or cytotoxic chemotherapy. Drug resistances for concomitant corticosteroids might be possible. In addition, steroids used in palliative care for a long time period (5) should be reconsidered, which may conversely accelerate the growth of prostate cancer.

The 'steroid switch' from prednisolone to dexamethasone at PSA progression might be feasible options, which may delay the development of the disease. The underlying mechanisms require further study. Although it is unclear whether the 'steroid switch' would contribute to the prognosis of the patient, the time to abiraterone failure was elongated through

'steroid switch' in our case. When the conditions of the patient allow, it would be acceptable to switch steroids for a brief period before starting further therapy.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

TK designed the study, contributed to analysis and interpretation of data, and wrote the initial draft of the manuscript. SK, AK and YN contributed to analysis and assisted in the preparation of the manuscript. KY contributed to pathological diagnosis. All authors, including AF, KO, TS, KH, KA and HM, have contributed to clinical management of the reported case. All authors critically reviewed the manuscript and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of the present case report and any accompanying images.

Competing interests

None declared under financial, general, and institutional competing interests.

References

1. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, Chi KN, Jones RJ, Goodman OB Jr, Saad F, *et al*: Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 364: 1995-2005, 2011.
2. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, Oudard S, Théodore C, James ND, Turesson I, *et al*: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 351: 1502-1512, 2004.
3. James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, Ritchie AW, Parker CC, Russell JM, Attard G, *et al*: Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): Survival results from an adaptive, multiarm, multistage, platform randomized controlled trial. *Lancet* 387: 1163-1177, 2016.
4. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, Özgüroğlu M, Ye D, Feyerabend S, Protheroe A, *et al*: Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med* 377: 352-360, 2017.
5. Leppert W and Buss T: The role of corticosteroids in the treatment of pain in cancer patients. *Curr Pain Headache Rep* 16: 307-313, 2012.

6. Khandwala HM, Vassilopoulou-Sellin R, Logethesis CJ and Friend KE: Corticosteroid-induced inhibition of adrenal androgen production in selected patients with prostate cancer. *Endocr Pract* 7: 11-15, 2001.
7. Eichholz A, Ferraldeschi R, Attard G and de Bono JS: Putting the brakes on continued androgen receptor signaling in castration resistant prostate cancer. *Mol Cell Endocrinol* 360: 68-75, 2012.
8. Komiya A, Shimbo M, Suzuki H, Imamoto T, Kato T, Fukasawa S, Kamiya N, Naya Y, Mori I and Ichikawa T: Oral low-dose dexamethasone for androgen-independent prostate cancer patients. *Oncol Lett* 1: 73-79, 2010.
9. Venkitaraman R, Lorente D, Murthy V, Thomas K, Parker L, Ahiabor R, Dearnaley D, Huddart R, De Bono J and Parker C: A randomised phase 2 trial of dexamethasone versus prednisolone in castration-resistant prostate cancer. *Eur Urol* 67: 673-679, 2015.
10. Lorente D, Omlin A, Ferraldeschi R, Pezaro C, Perez R, Mateo J, Altavilla A, Zafeiropoulos Z, Tunariu N, Parker C, *et al*: Tumour responses following a steroid switch from prednisone to dexamethasone in castration resistant prostate cancer patients progressing on abiraterone. *Br J Cancer* 111: 2248-2253, 2014.
11. Schmid S, Fornaro J, Rothermundt C, Omlin A, Brändle M, Rupp NJ and Gillissen S: Abiraterone-what is wrong with the adrenal glands? *Clin Genitourin Cancer* 12: e133-e137, 2014.
12. Tannock I, Gospodarowicz M, Meakin W, Panzarella T, Stewart L and Rider W: Treatment of metastatic prostatic cancer with low-dose prednisone: Evaluation of pain and quality of life as pragmatic indices of response. *J Clin Oncol* 7: 590-597, 1989.
13. Venkitaraman R, Thomas K, Huddart RA, Horwich A, Dearnaley DP and Parker CC: Efficacy of low-dose dexamethasone in castration-refractory prostate cancer. *BJU Int* 101: 440-443, 2008.
14. De Santis M and Saad F: Practical guidance on the role of corticosteroids in the treatment of metastatic castration resistant prostate cancer. *Urology* 96: 156-164, 2016.
15. Weitzman AL, Shelton G, Zuech N, Owen CE, Judge T, Benson M, Sawczuk I, Katz A, Olsson CA, Bagiella E, *et al*: Dexamethasone does not significantly contribute to the response rate of docetaxel and estramustine in androgen independent prostate cancer. *J Urol* 163: 834-837, 2000.
16. Diederich S, Scholz T, Eigendorff E, Bumke-Vogt Ch, Quinkler M, Exner P, Pfeiffer AF, Oelkers W and Bähr V: Pharmacodynamics and pharmacokinetics of synthetic mineralocorticoids and glucocorticoids: Receptor transactivation and prereceptor metabolism by 11 β -hydroxysteroid-dehydrogenases. *Horm Metab Res* 36: 423-429, 2004.
17. Nishimura K, Nonomura N, Yasunaga Y, Takaha N, Inoue H, Sugao H, Yamaguchi S, Ukimura O, Miki T and Okuyama A: Low doses of oral dexamethasone for hormone-refractory prostate carcinoma. *Cancer* 89: 2570-2576, 2000.
18. Crona DJ and Whang YE: Androgen receptor-dependent and -independent mechanisms involved in prostate cancer therapy resistance. *Cancers (Basel)* 9: pii: E67, 2017.
19. Arora VK, Schenkein E, Murali R, Subudhi SK, Wongvipat J, Balbas MD, Shah N, Cai L, Efstathiou E, Logothetis C, *et al*: Glucocorticoid receptor confers resistance to antiandrogens by bypassing androgen receptor blockade. *Cell* 155: 1309-1322, 2013.
20. Lan NC, Graham B, Bartter FC and Baxter JD: Binding of steroids to mineralocorticoid receptors: Implications for in vivo occupancy by glucocorticoids. *J Clin Endocrinol Metab* 54: 332-342, 1982.
21. Dovic A, Sartori ML, De Francia S, Mussino S, Perotti P, Saba L, Abbadessa G, Racca S and Angeli A: Differential expression of determinants of glucocorticoid sensitivity in androgen-dependent and androgen-independent human prostate cancer cell lines. *J Steroid Biochem Mol Biol* 116: 29-36, 2009.
22. Leach DA, Powell SM and Bevan CL: Women in Cancer Thematic Review: New roles for nuclear receptors in prostate cancer. *Endocr Relat Cancer* 23: T85-T108, 2016.
23. Taplin ME, Bubley GJ, Shuster TD, Frantz ME, Spooner AE, Ogata GK, Keer HN and Balk SP: Mutation of the androgen-receptor gene in metastatic androgen-independent prostate cancer. *N Engl J Med* 332: 1393-1398, 1995.
24. Zhao XY, Malloy PJ, Krishnan AV, Swami S, Navone NM, Peehl DM and Feldman D: Glucocorticoids can promote androgen-independent growth of prostate cancer cells through a mutated androgen receptor. *Nat Med* 6: 703-706, 2000.
25. Richards J, Lim AC, Hay CW, Taylor AE, Wingate A, Nowakowska K, Pezaro C, Carreira S, Goodall J, Arlt W, *et al*: Interactions of abiraterone, eplerenone, and prednisolone with wild-type and mutant androgen receptor: A rationale for increasing abiraterone exposure or combining with MDV3100. *Cancer Res* 72: 2176-2182, 2012.
26. Nishimura K, Nonomura N, Satoh E, Harada Y, Nakayama M, Tokizane T, Fukui T, Ono Y, Inoue H, Shin M, *et al*: Potential mechanism for the effects of dexamethasone on growth of androgen-independent prostate cancer. *J Natl Cancer Inst* 93: 1739-1746, 2001.
27. Lam JS, Leppert JT, Vemulapalli SN, Shvarts O and Belldgrun AS: Secondary hormonal therapy for advanced prostate cancer. *J Urol* 175: 27-34, 2006.
28. Yano A, Fujii Y, Iwai A, Kageyama Y and Kihara K: Glucocorticoids suppress tumor angiogenesis and in vivo growth of prostate cancer cells. *Clin Cancer Res* 12: 3003-3009, 2006.
29. Akakura K, Suzuki H, Ueda T, Komiya A, Ichikawa T, Igarashi T and Ito H: Possible mechanism of dexamethasone therapy for prostate cancer: Suppression of circulating level of interleukin-6. *Prostate* 56: 106-109, 2003.
30. Ueda T, Bruchovsky N and Sadar MD: Activation of the androgen receptor N-terminal domain by interleukin-6 via MAPK and STAT3 signal transduction pathways. *J Biol Chem* 277: 7076-7085, 2002.