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LETTER TO THE EDITOR

Prostate Cancer

Response of prostate cancer to addition of dutasteride after progression on abiraterone

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Dear Editor,

Abiraterone has achieved great success in clinic by targeting cytochrome P450 17A1 (CYP17A) for prostate cancer therapy.^{1,2} However, drug resistance is inevitable and novel strategy is urgently required. Our previous work unveils a steroidal metabolic pathway for abiraterone in patients.^{3,4} Steroidogenic enzyme 3 β -hydroxysteroid dehydrogenase 1 (3 β HSD1) catalyzes abiraterone to Δ^4 -abiraterone (D4A), which is further catalyzed to 5 α -abiraterone (5 α -Abi) by steroid-5 α -reductase (SRD5A). The metabolite 5 α -Abi binds to androgen receptor (AR) directly and activates AR signaling.⁴ This metabolic pathway not only reduces plasma concentration of abiraterone, but also generates a mild AR agonist, which might cause drug resistance. Dutasteride, as a potent SRD5A inhibitor, suppresses the conversion from D4A to 5 α -Abi and might be used to enhance abiraterone efficiency (Figure 1a).⁴ However, this function of dutasteride has not been proved in clinic. Here, we report the effect of dutasteride plus abiraterone treatment in two abiraterone-resistant patients.

Two metastatic castration-resistant prostate cancer (mCRPC) patients after abiraterone resistance were recruited in a clinical research for the combination therapy (dutasteride and abiraterone plus prednisone) at Tongji Hospital (Shanghai, China) with signed informed consent, following a protocol approved by the Ethics Committee of Tongji Hospital (ChiCTR1800015510). The clinical characteristics of patients at diagnosis are listed in Supplementary Table 1. They progressed to mCRPC in 20 months (#W7546) and 12 months (#D3459), respectively. The serum testosterone level was consistently lower than 20 ng dl⁻¹ even after abiraterone resistance. Considering of the dynamics of abiraterone metabolism, plasma samples were collected approximately 3 h after abiraterone administration.⁵ A liquid chromatography-mass spectrometry (LC-MS) method was established with minor modification of our previous protocol to detect all 8 abiraterone metabolites at the same time (Supplementary Method for details).⁶

The patient #W7546 received abiraterone (1000 mg once daily), prednisone (5 mg twice daily), and dutasteride (0.5 mg once

daily), at the same time in the morning, which we short named as APD, according to the clinic protocol. Previously, he responded to abiraterone for more than 3 months with maximum prostate-specific antigen (PSA) reduction of 80% (Figure 1b and 1c). However, his PSA increased dramatically after abiraterone resistance (day 102–161). He received the combination therapy since day 188 and the increase of PSA was halted. The addition of dutasteride led to a maximum PSA reduction of 23.0% and extended the response to abiraterone for 2–3 months (Figure 1b and 1c). The effect of dutasteride on abiraterone metabolism was confirmed by the increase of plasma abiraterone and the reduction to 0 of plasma 5 α -Abi and its downstream metabolites. These data together indicate that dutasteride enhances abiraterone efficacy in this patient.

Dutasteride was administered to the patient #D3459 since day 243. He received abiraterone and prednisone in the morning but dutasteride in the afternoon (AP+D) for the first 4 months due to gastrointestinal irritation and then changed to the standard protocol (APD) as the patient #W7546. The patient #D3459 responded to abiraterone for more than 5 months with a maximum PSA reduction of 95.8% (Figure 1d). The AP+D therapy showed no effect on PSA until 63 days later. The effect of dutasteride on abiraterone metabolism in this patient was gradually achieved as indicated by the increase of plasma Abi and reduction to 0 of 5 α -Abis 63 days after the addition of dutasteride. Although no significant PSA reduction after the combination therapy, the addition of dutasteride held PSA increase for approximately 130 days.

Currently, there is no efficient therapy for abiraterone-resistant mCRPC. Dutasteride itself shows mild effect for prostate cancer therapy but might be used together with other drugs.^{7,8} Here, we show that dutasteride enhances abiraterone clinical efficacy in two abiraterone-resistant patients. The addition of dutasteride extended PSA doubling time and led to PSA reduction. The increase of plasma abiraterone and reduction of 5 α -Abis might be clinical indicators for the efficiency of dutasteride. Notably, the patient #W7546 responded to the combination therapy more quickly than the patient #D3459 as indicated by the alteration of PSA. It might result from patient heterogeneity. The differences in drug administration (APD vs AP+D) might also contribute to the clinical divergence. Previous investigation on abiraterone pharmacokinetics indicates that plasma abiraterone has decreased significantly and the major metabolites have been generated already 6 h after drug administration. Thus, dutasteride might not be

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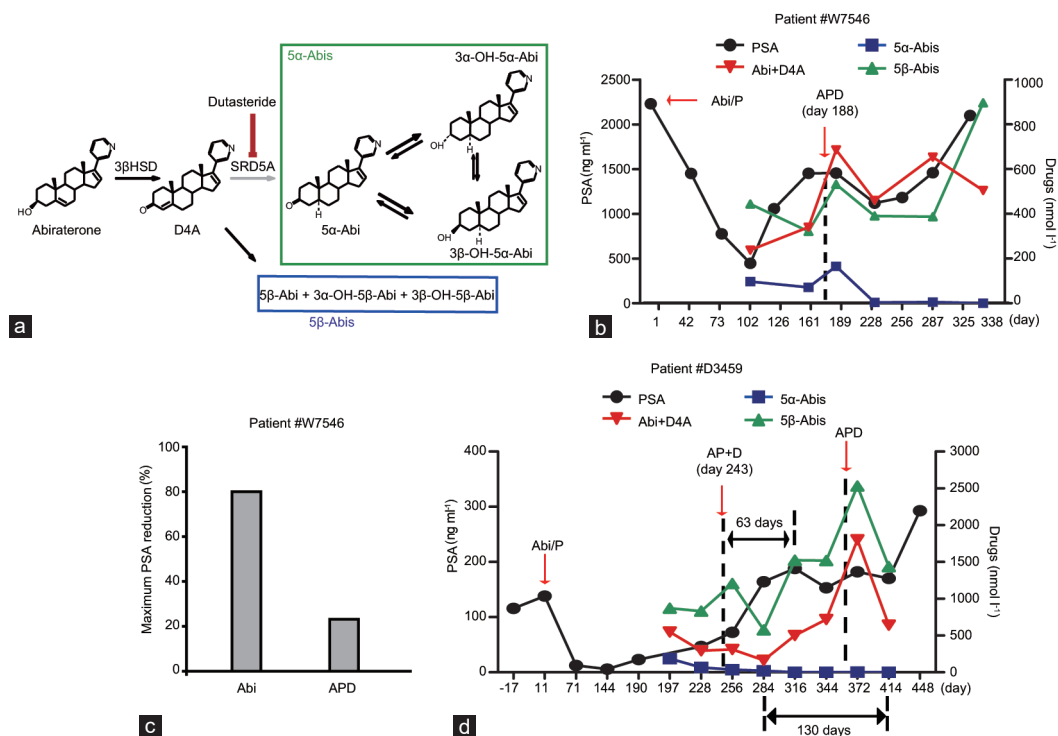


Figure 1: Dutasteride enhances the efficacy of abiraterone in two abiraterone-resistant patients. (a) Schema of dutasteride function in abiraterone metabolism. (b) Alteration of PSA and plasma abiraterone metabolites in patient #W7546. 5 α -Abis, 5 α -Abi + 3 α -OH-5 α -Abi + 3 β -OH-5 α -Abi; 5 β -Abis, 5 β -Abi + 3 α -OH-5 β -Abi + 3 β -OH-5 β -Abi. (c) Maximum PSA reduction of patient #W7546 when treated with abiraterone alone or together with dutasteride. (d) Alteration of PSA, plasma abiraterone metabolites in patient #D3459. PSA: prostate-specific antigen; D4A: Δ^4 -abiraterone; 3 β HSD1: steroidogenic enzyme 3 β -hydroxysteroid dehydrogenase 1; Abi: abiraterone; Abi/P: abiraterone plus prednisone treatment; APD: abiraterone/prednisone and dutasteride taken at the same time; AP+D: abiraterone/prednisone and dutasteride taken separately.

able to effectively affect abiraterone metabolism when taking separately (AP+D). However, dutasteride has a long half-life in patients (10 days to 5 weeks), which is helpful for abiraterone metabolism regulation after enough accumulation.⁹

Together, these data demonstrate that dutasteride is capable to regulate abiraterone metabolism to benefit some abiraterone-resistant patients. The main limitation of the present case report is the limited number of patients. Future clinical research with more patients to confirm the clinical effect of the combination therapy after abiraterone resistance is in progress.

AUTHOR CONTRIBUTIONS

SSH and ZFL conceived and designed the study. JPL, XC, YL, and DLW collected the clinical data. YYG and JJT detected plasma abiraterone metabolites. SSH and ZFL wrote the manuscript. All authors have read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

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Supplementary Information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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