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# High-dose itraconazole as a non-castrating therapy for a patient with biochemically-recurrent prostate cancer

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### Keywords

Itraconazole; biochemical recurrence; prostate cancer; Hedgehog pathway

## Introduction

Optimal management of patients with biochemically-recurrent prostate cancer after local therapy is controversial. Although treatment with androgen deprivation therapy (ADT) is considered standard in men with metastatic disease, the role of ADT for biochemical recurrence is less clear and there are limited therapeutic options that can delay disease progression or improve survival in these patients. Furthermore, ADT is associated with significant adverse effects including fatigue, hot flashes, loss of libido, loss of bone mineral density, sarcopenia, increased adiposity, metabolic abnormalities, and increased risk of coronary artery disease and other vascular complications.[1,2] Thus, there is interest in developing non-castrating therapies in this setting that can improve clinical outcomes.

Itraconazole is an FDA-approved antifungal drug used in the treatment of various mycoses that was repurposed as an antineoplastic agent after a screening effort identified that it could potently inhibit Hedgehog (Hh) pathway signaling in cancer.[3] Following from preclinical studies, a phase II clinical trial suggested that itraconazole prescribed at high doses (600 mg per day) may have a role as an antineoplastic agent in men with metastatic castration-resistant prostate cancer (CRPC) who had not previously received chemotherapy.[4] In this trial, modest clinical activity using high-dose itraconazole in this setting was demonstrated as evidenced by longer PSA-progression-free survival and clinical/radiographic-progression-free survival compared to historical controls. Of note, treatment with itraconazole did not appear to have a significant effect on testosterone levels in these men with CRPC, suggesting that its clinical activity (unlike that of ketoconazole) may be independent of androgen modulation.



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To date, the clinical and endocrine effects of itraconazole in men with non-castrate biochemically-recurrent prostate cancer are unknown. Here, we describe a case of a patient with biochemical recurrence treated with high-dose itraconazole who achieved a PSA response that was not associated with androgen suppression.

## Case report

A 65-year-old man presented with biochemical recurrence of prostate cancer. He was initially diagnosed with prostate cancer in 2004 after developing an elevated PSA reading. At the time of initial diagnosis, he had clinical stage T1c disease and a prostate biopsy demonstrated adenocarcinoma with Gleason score 3+4=7. He underwent radical prostatectomy in January 2005 which demonstrated Gleason 4+3=7 prostate adenocarcinoma associated with extraprostatic extension and node-negative disease, yielding a final pathological stage of $T_{3a}N_0M_0$. Following prostatectomy, his PSA was initially undetectable, but then became detectable in March 2006 and subsequently rose gradually with a PSA doubling time (PSADT) of approximately 7 months. In September 2009, he underwent salvage external-beam radiation therapy, but his PSA continued to rise following radiotherapy. In October 2012, he was referred to our institution for non-hormonal management of his biochemically-recurrent prostate cancer, at which time his PSA was 34.3 ng/mL and his PSADT was about 6 months. MRI of his abdomen/pelvis, CT of the chest and abdomen/pelvis, and whole-body technetium-99 bone scan were all negative for radiographic metastatic disease. Due to the patient's strong desire to avoid castrating therapies, he requested to be treated off-study with high-dose itraconazole based on the results of the prior phase II trial, while he voiced understanding that this study was conducted in a different patient population and that the results may not apply to his current disease state.

At initiation of treatment with itraconazole (300 mg, twice daily), the patient's PSA level was 34.3 ng/mL and his testosterone level was in the non-castrate range (Fig. 1). Dehydroepiandrosterone (DHEA), a testosterone precursor, was also in the normal range. Given the potential concern for itraconazole-mediated suppression of adrenal cortical function, aldosterone and cortisol levels were also evaluated as were ACTH levels. Following only one month of treatment with itraconazole, the PSA declined to 20.1 ng/mL, while the patient did report some grade-1 fatigue. After three months of treatment, his PSA had declined to 16.2 ng/mL, reflecting a >50% PSA reduction. Importantly, his testosterone levels remained largely unchanged, while DHEA levels increased somewhat. The patient had no clinical or biochemical evidence of adrenal insufficiency or hypocortisolism. Conversely, he developed hypoaldosteronism accompanied by an elevation in ACTH (Fig. 1), consistent with the experience from the prior phase II study.[4] After 5 months of treatment, and despite a persistent PSA response with minimal adverse events, the patient developed asymptomatic hyperbilirubinemia necessitating discontinuation of itraconazole. While the bilirubin level normalized after stopping itraconazole, this was accompanied by a subsequent increase in PSA level to 29.4 ng/mL, approximately one month after drug discontinuation. Due to the occurrence of hyperbilirubinemia, further treatment with high-dose itraconazole was discouraged.

## Discussion

High-dose itraconazole (600 mg/day) has demonstrated modest clinical activity in men with metastatic castration-resistant prostate cancer.[4] Its efficacy in that setting appeared to be independent of testosterone or DHEA suppression, although all men in that study also continued on treatment with standard ADT and had "castrate" serum testosterone levels at study entry. The present case report allows us to examine the clinical and endocrine effects

of itraconazole in a man with non-castrate androgen levels as well as non-metastatic disease. In this patient with biochemically-recurrent prostate cancer, high-dose itraconazole produced a >50% PSA decline without suppression of testosterone or DHEA levels. Another azole antifungal, ketoconazole, has been used off-label for many years as a therapy for CRPC; however, that agent appears to function by suppressing extragonadal androgen synthesis through non-selective inhibition of multiple $CYP_{450}$ enzymes including CYP17.[5] Therefore, the present report lends further credence to the hypothesis that itraconazole has clinical efficacy in prostate cancer that is independent of androgen suppression, even in the non-castrate setting as demonstrated here.

It is becoming increasingly understood that itraconazole may function as an antineoplastic agent when given at high doses. Beachy and colleagues screened 2400 known pharmacologic compounds to identify itraconazole as an inhibitor of the Hedgehog pathway in several cancer models. Further work revealed that itraconazole is a strong inhibitor of cell proliferation in a Hh reporter cell line and functions via attenuation of Smoothened (SMO) activity.[3] Importantly, Hh-inhibitory activity was not seen with the other azole antifungal agents tested (*e.g.* ketoconazole was 12 times less potent in this regard). In addition, itraconazole showed tumor growth inhibition in a mouse model of medulloblastoma that has constitutive overactivation of Hh signaling.[3] In this mouse model, the serum levels of itraconazole required for tumor inhibition were equivalent to those achieved in man using 600 mg of oral itraconazole daily, hence the dose selected for clinical development of itraconazole in cancer. These studies demonstrated that itraconazole is an effective inhibitor of Hh signaling both *in vitro* and *in vivo.*

In the prior phase II clinical trial conducted in men with metastatic CRPC, itraconazole treatment was associated with down-modulation of Hh signaling as assessed by expression of *GLI1* mRNA levels in a surrogate tissue (normal skin).[4] The Hedgehog pathway regulates epithelial and mesenchymal interactions in a variety of tissues during mammalian embryogenesis.[6] Many of its target genes are involved in cell proliferation, survival and angiogenesis; and Hh signaling has been implicated in prostate cancer progression as well as androgen resistance.[7–9] Itraconazole-mediated suppression of Hh signaling thus represents a promising potential mechanism for the clinical activity seen in human subjects with prostate cancer. Additional trials are currently being designed to further investigate the role of potent suppression of Hh signaling in men with CRPC. In addition, a formal phase II study is currently underway evaluating high-dose itraconazole in men with non-castrate biochemically-recurrent prostate cancer (NCT01787331).

## Conclusion

Non-castrating therapies with a distinct mechanism of action from those targeting the androgen receptor axis, such as itraconazole, represent a promising future option for the treatment of both biochemically-recurrent and advanced prostate cancer.

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### Clinical Practice Points

- The role of androgen deprivation therapy in biochemically-recurrent prostate cancer is unclear and is associated with significant adverse events.
- Itraconazole has demonstrated clinical activity in castration-resistant prostate cancer and does not appear to mediate its activity by androgen suppression.
- In this patient with biochemically-recurrent prostate cancer, off-label treatment with itraconazole (600 mg/day) resulted in a >50% decline in PSA, without evidence of testosterone suppression.
- Inhibition of the Hedgehog pathway may mediate the clinical activity of itraconazole. Clinical trials are ongoing to further elucidate this mechanism in men with biochemically-recurrent and castration-resistant prostate cancer.

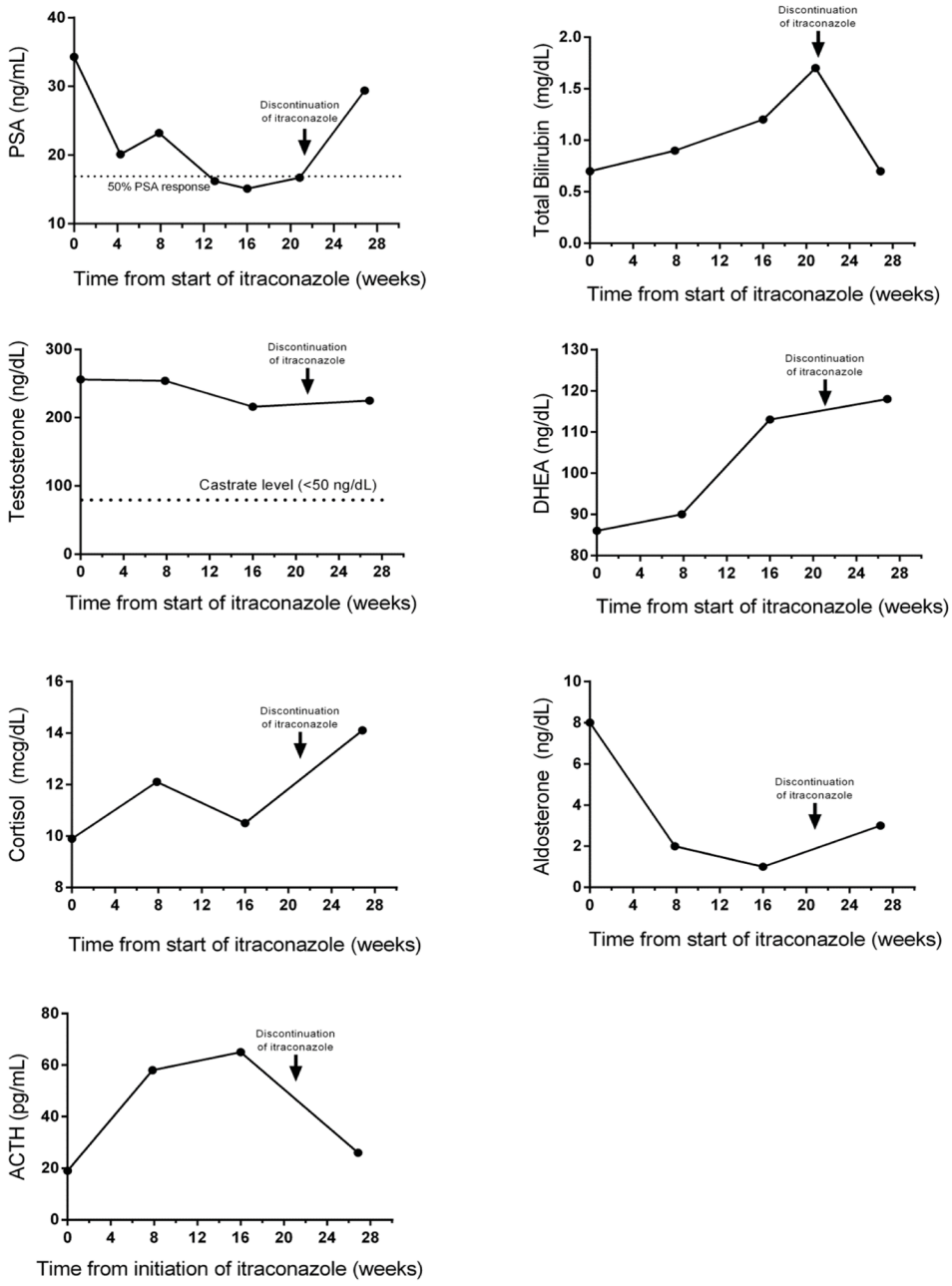


**Figure 1.**

The patient achieved a 50% reduction in PSA after administration of high-dose itraconazole. Testosterone levels remained in the non-castrate range, while DHEA levels paradoxically increased. Clinically and biochemically, the patient demonstrated no evidence of hypocortisolism or adrenal insufficiency. In fact, itraconazole treatment resulted in hypoaldosteronism and an elevation of ACTH levels. Hyperbilirubinemia developed after 5 months of itraconazole treatment, but resolved after drug discontinuation.