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Abbreviations: **CRPC**, castration-resistant prostate cancer; **CR + PR + SD**, complete response + partial response + stable disease.

EDITORIAL COMMENT

SECONDARY HORMONAL MANIPULATIONS IN THE TREATMENT OF CASTRATION REFRACTORY PROSTATE CANCER

The cornerstone of treatment for advanced prostate cancer is medical or surgical castration i.e. androgen deprivation therapy (ADT). Despite initial responses, almost all patients develop castration refractory prostate cancer (CRPC). In CRPC, most tumors remain dependent on androgen receptor (AR) signaling for proliferation [1] and many CRPC patients will continue to respond, to sequential administration of secondary hormonal manipulations [2].

In this paper, Procopio *et al.* report on the efficacy of low dose ketoconazole (200 mg orally every eight hours) in a phase 2, single

arm study of 37 patients with CRPC. The primary endpoint was PSA response, which was defined as partial response (PR) i.e. PSA ≤50% or complete response (CR) i.e. undetectable PSA. There were two CRs and 6 PRs, with an overall PSA response rate of 21%. These included one CR and four PRs in 15 patients with prior chemotherapy. However the median duration of benefit was only 21 weeks (5 months) similar to prior reports of low dose ketoconazole [3].

It is of interest that 31 of 37 patients had measurable disease, yet no objective responses (OR) were observed. Using PSA response as stand-alone criteria has no meaning with respect to response, and has been misconstrued as suggestive of clinical benefit [4]. Therefore, the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) has recommended that the reporting of PSA response rates be avoided and that the maximal PSA decline/patient be reported in a waterfall plot. Waterfall plots allow a given data set to be analyzed on the basis of any degree of decline and to be compared to other trials [4].

Ketoconazole has a weak and non-specific inhibitory affect on several enzymes involved in androgen synthesis and has been widely used in combination with hydrocortisone for the treatment of CRPC [2]. However, ketoconazole is associated with significant toxicities. The effect of ketoconazole on overall survival is difficult to discern [5]. In a phase 3 study of 260 patients with CRPC, PSA responses and ORs were significantly higher with a combination of ketoconazole-hydrocortisone and antiandrogen withdrawal (AAWD) when compared to AAWD alone. There was no difference in median survival (~16 months for both arms of the study) [6]. Higher baseline androstenedione levels were predictive of response to ketoconazole but were not prognostic [1]. Low dose ketoconazole (200 mg orally thrice daily) has also been shown to be associated with PSA responses comparable to standard dose ketoconazole but no comparative studies of standard versus low dose have been done [7].

Recognition of the role of continued AR signaling in disease progression in CRPC has led to the development of newer drugs such as abiraterone and MDV 3100. Abiraterone acetate (Johnson & Johnson, New Brunswick, NJ), is an orally administered pregnenolone analog that irreversibly inhibits CYP17 (a key enzyme in androgen synthesis) and blocks the synthesis of androgens in the testes, adrenal glands and prostate, without causing adrenal insufficiency [1]. MDV 3100 (Medivation Inc, San Francisco, CA) is an orally administered novel AR antagonist that binds to AR with a much higher affinity (eight times higher) than bicalutamide and blocks nuclear translocation of AR and DNA binding [5]. Based on the promising results of phase 2 clinical trials, there are currently several ongoing phase 3 studies of abiraterone and MDV 3100 in patients with progressive CRPC, with results expected in near future. Until more promising treatment options become available, ketoconazole remains a pertinent option in patients with CRPC when clinical trials are not an option.

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