Original Article

Efficacy of Low-dose Ketoconazole in Hormone Refractory Prostate Cancer Patients at the National Cancer Centre and The Cancer Institute, Singapore

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Abstract

Introduction: The advent of prostate specific antigen (PSA) has resulted in an increased incidence of early detection of prostate cancer recurrence. Patients treated with androgen deprivation therapy (ADT) become hormone-resistant after 18 to 24 months. In patients with biochemical failure, where there is a rise in PSA but no objective evidence of metastases, or in whom there are small volume metastases but who are asymptomatic, there is no standard of care after ADT. Ketoconazole, an antimycotic which affects the synthesis of androgens and other steroids, has shown direct cytotoxic effects in prostate cancer cell lines in in-vitro studies. This study describes our experience with ketoconazole treatment for hormone refractory prostate cancer (HRPC). Materials and Methods: A retrospective study of HRPC patients given ketoconazole at the National Cancer Centre and The Cancer Institute from 2004 to 2005 was performed. All eligible patients had histologically proven adenocarcinoma of the prostate and a rising PSA level despite ADT with orchidectomy or luteinising hormone-releasing hormone (LHRH) agonist therapy. All patients received 200 mg of ketoconazole thrice daily. Response was defined as a decline in PSA of at least 50% from the pre-treatment level and confirmed by a second PSA value 4 or more weeks later. The endpoints evaluated were the presence and duration of a response and the toxicity profile of the treatment. Results: A total of 32 patients with HRPC were treated with ketoconazole. Twelve (38%) of the 32 patients had a greater than 50% decrease in their PSA values. The median duration of response was 6.75 months. The median time to reach PSA nadir was 3.5 months. Five patients continue to exhibit progression-free response at the time of writing. Ketoconazole was generally well tolerated. Eighteen (56%) patients recorded mild toxicities related to ketoconazole. There were no grade 3 or 4 toxicities. Conclusions: Low-dose ketoconazole bridges the gap in the continuum of treatment for patients who have failed ADT and in whom cytotoxic chemotherapy would have a significant impact on the quality of life. Its good toxicity profile, low cost and ease of administration makes it a viable option for this group of patients.

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Introduction

Prostate cancer is the fifth most frequent malignancy among Singapore males, with the incidence rising steadily over the years.[1] With the advent of prostate specific antigen (PSA), the incidence of prostate cancer is not only on the rise, but disease recurrence can also be detected earlier. PSA detects a subset of patients with biochemical failure, defined as a rising PSA without objective evidence of metastasis after treatment for localised disease. Although some of these patients are treated conservatively, others are started early on androgen deprivation therapy (ADT) due to the presence of poor prognostic factors or due to patients' or even physicians' psychological inability to accept a conservative approach. Despite ADT's high response rate of 80% to 90%, these patients will eventually become hormone resistant, with a progression-free duration of 18 to 24 months. Docetaxel-based chemotherapy is effective in hormone refractory prostate cancer (HRPC) with a survival advantage when used as a first-line treatment. It is now considered the standard of care in metastatic HRPC.[2,3]

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However, in patients with small volume metastasis where early chemotherapy is not warranted, in patients with biochemical failure only, or in patients who refuse chemotherapy, management remains controversial as there is no universally accepted treatment protocol. Therefore, there is a void in the management of these patients.

Ketoconazole is an antimycotic that inhibits cytochrome P450 enzymes, which are required for the synthesis of androgens and other steroids. In-vitro studies have suggested some direct cytotoxic effects in prostate cancer cell lines as well.[4,5] Studies of ketoconazole done during the pre-PSA era have shown response rates of 11% to 13% and disease stabilisation in 37% to 50% of patients accompanied by marked palliation of pain.[6,7] Current studies using PSA as a marker of response showed a greater than 50% decrease in PSA in 40% to 63% of HRPC patients given high-dose ketoconazole (HDK) at 400 mg thrice daily.[8-13] The median duration of response was 6 months.[9,10] A phase III trial using HDK with anti-androgen withdrawal (AAWD) versus AAWD alone reported PSA responses of 27% and 11% respectively, with time to PSA progression 8.6 months in responders.[11] However, significant toxicities such as grade 3 to 4 neurotoxicity, lassitude and hepatic toxicity are reported in these studies. One approach to reduce toxicity is to use lower doses of ketoconazole. A phase II trial by Harris et al[12] using low-dose ketoconazole at 200 mg thrice daily showed a response rate of 46% with fewer side effects, while another trial had a 55% response rate with ketoconazole at 300 mg thrice daily.[14]

This study aims to describe the experience with ketoconazole treatment for HRPC at the National Cancer Center and The Cancer Institute of Singapore.

Materials and Methods

A retrospective chart review of HRPC patients given ketoconazole at the National Cancer Center and The Cancer Institute's Department of Medical Oncology from 2004 to 2005 was done. All patients had histologically proven adenocarcinoma of the prostate with rising PSA despite ADT with orchidectomy or LHRH agonist therapy. Anti-androgens had to be withdrawn for at least 6 weeks before the start of ketoconazole. Patients who were on maintenance LHRH agonist must have proven castrated level of testosterone.

Ketoconazole was given at 200 mg thrice daily. Replacement doses of oral hydrocortisone or prednisolone were given in 19 out of 32 evaluable patients. Patients had monthly follow-up visits to evaluate for toxicities or adverse events. Complete blood counts, liver function tests and PSA were done monthly. Response was defined as a PSA decline of at least 50% from the pre-treatment level and confirmed by a second PSA value 4 or more weeks later.[15,16] Endpoints determined include the response rate, duration of response and toxicity profile.

Results

A total of 32 patients with HRPC were treated and evaluable for response and toxicity. The pretreatment characteristics of the patients are shown in Table 1. The median age was 70 years (range, 53 to 85). Fourteen had bone-only disease, 13 had bone and soft tissue disease, 2 had soft tissue-only disease, 1 had bone and lung disease and 2 had PSA-only disease. The baseline of PSA ranged from 2.51 to 2500 ug/mL at the start of ketoconazole.

Response Rate

Twelve (38%) of the 32 patients had a PSA response with ketoconazole as defined by at least 50% reduction in the PSA level from its baseline. Responses were seen in 43% (6 out of 14) of patients with bone-only disease, 31% (4 out of 13) of patients with bone and soft tissue disease and in both the patients with PSA-only disease (Table 2). The median duration of response was 6.75 months (range, 2 to 14). The median time to reach PSA nadir was 3.5 months (range, 1.5 to 11). Five patients remained progression-free at the time of writing. Three of the 12 responders had the dose of ketoconazole increased to 400 mg thrice daily following a subsequent rise in PSA after the initial response. All 3 patients experienced another PSA response. The median duration of this response was 7 months, 8 months and 9 months respectively. The total duration of response for each of the 3 patients was 11 months, 14 months and 13 months respectively.

Adverse Effects

Ketoconazole was generally well tolerated. Overall, 18 (56%) patients had recorded toxicities related to ketoconazole, most of which were mild (Table 3). Two

Table 1. Pretreatment Characteristics (n = 32)

Age (y)	
Median	70
Range	53-85
Extent of disease	
Bone only	14
Bone and soft tissue	13
Soft tissue only	2
Bone and lungs	1
PSA only	2
PSA at entry	
Range	2.51-2500 ug/mL

PSA: prostate specific antigen

Table 2. Characteristics of Responders

Patient	Age (y)	Site of metastasis	Baseline PSA level	PSA nadir	Time To PSA nadir (mo)	Duration of ketoconazole (mo)
1	61	Bone and Liver	33.1	13	1.5	3
2	73	Bone	42.8	13.7	2	2
3	83	Bone	302	83	3	3
4	63	Bone	33.1	0.4	10	13
5	75	Lung and Bone	122	49	2	2
6	65	PSA only	114	26.7	5	7
7	70	Bone	58.5	4.3	11	14
8	71	Bone and Lymph node	>2500	246	6	14
9	64	Bone	55.6	0.3	3.5	8
10	75	Bone and Lymph node	196.1	58.2	2	4
11	69	Bone	344.2	124.1	3.5	12
12	56	PSA only	65.87	6.93	7	11
						Total: 93
						Mean: 7.75

PSA: prostate specific antigen

Table 3. Adverse Events

Toxicities	No. (%)
Grade 1 transaminitis	12 (38)
Grade 2 transaminitis	1 (3)
Giddiness	2 (6)
Flushing	1 (3)
Gastrointestinal	3 (9)
Oedema	1 (3)
Fatigue	1 (3)
Easy bruisability	1 (3)
Rashes	1 (3)

patients experienced giddiness, for which a replacement steroid was administered for presumed symptomatic adrenal suppression. Twelve patients had grade 1 elevations in transaminases while 1 patient had grade 2 elevation. Transaminitis normalised upon stopping the drug. One patient had flushing. Three patients had mild gastrointestinal toxicities. One patient had mild peripheral oedema, 1 had mild fatigue, 1 had easy bruisability and 1 had a non-specific rash that reversed upon stopping medication. One patient discontinued the drug as a result of hypoglycaemia.

Discussion

The management of prostate cancer has been undergoing a paradigm shift. This includes stage migration, with more asymptomatic, lower stage cancers diagnosed due to the availability of PSA testing. Similarly, more recurrences are diagnosed earlier and androgen ablative therapy started earlier with a median duration of response of 18 to 24 months. While second-line hormonal therapy with anti-androgens (bicalutamide, flutamide) is a common approach in cases with progression after androgen ablation, we sense that the role of ketoconazole in HRPC is less well known in the local scene. Chemotherapy has been approved for symptom palliation in prostate cancer since 1996 and has recently also been proven to increase overall survival. However, patients with advanced prostate cancer requiring chemotherapy may be elderly, have poor performance status or poor organ function, which excludes them from chemotherapy. Others, for personal reasons, may refuse chemotherapy or prefer to delay it. Ketoconazole provides a convenient oral therapeutic option, which is not only affordable but fairly non-toxic as well. We noted a 38% PSA response in this retrospective study of low-dose ketoconazole in HRPC patients, a result comparable to the 46% response rate reported by Harris et al,[12] hence underlining the respectable efficacy of ketoconazole in prostate cancer management.

Replacement doses of hydrocortisone or prednisolone are often given to patients on ketoconazole, as ketoconazole is a potent inhibitor of adrenal steroid synthesis. Corticosteroid itself exhibits anti-tumour effects by ACTH inhibition via negative feedback. This results in decreased androgen production in the adrenal glands. Hydrocortisone and prednisolone have shown 16% to 22% PSA response although 1 study using dexamethasone showed 61% PSA response.[17] There are no randomised trials to say which of the above steroids is the most effective. In our study,

steroids were administered to 59% of patients. While steroids may have an additive effect on ketoconazole's efficacy, we believe that our result of 38% PSA response rate was due mainly to the activity of ketoconazole.

Toxicities were mild in our study. Although 56% of the patients reported adverse effects, they were generally manageable and only 1 discontinued the drug. This is in contrast to the studies on HDK where grade 3 to 4 toxicities were noted more often, thus necessitating the discontinuation of treatment.[9,10,18] Symptoms of adrenal insufficiency were seen in 2 out of 15 (13%) patients who were initially not given steroids. Hence, adrenal suppression may still occur in a small proportion of patients at a ketoconazole dose of 200 mg 3 times a day and there should be a low threshold for administering replacement doses of steroids to patients who are symptomatic.

Some limitations of this study include the limited number of patients evaluated and the fact that quality of life was not assessed.

Conclusion

Low-dose ketoconazole bridges the gap in the continuum of treatment for patients with biochemical failure who have failed ADT and in HRPC with small volume metastasis where cytotoxic chemotherapy would have a significant impact on quality of life. Its good toxicity profile, low cost and ease of administration make it a viable option for this group of patients. Further studies are needed to explore this aspect of HRPC. We await the results of a study by the Eastern Cooperative Oncology Group (ECOG) 1899, which is a phase III randomised trial evaluating second-line hormonal therapy (ketoconazole/hydrocortisone) versus combination chemotherapy (docetaxel/estramustine) on progression-free survival in HRPC patients.[19]

REFERENCES

1. Seow A, Koh WP, Chia KS, Shi LM, Lee HP, Shanmugaratnam K. Trends in Cancer Incidence in Singapore 1968-2002. Singapore: Singapore Cancer Registry, 2004.
2. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502-12.
3. Petrylak DP, Tangen CM, Hussain MH, Lara PN Jr, Jones JA, Taplin ME, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004;351:1513-20.
4. Rochlitz CF, Damon LE, Russi MB, Geddes A, Cadman EC. Cytotoxicity of ketoconazole in malignant cell lines. Cancer Chemother Pharmacol 1988;21:319-22.
5. Eichenberger T, Trachtenberg J, Toor P, Keating A. Ketoconazole: a possible direct cytotoxic effect of prostate carcinoma cells. J Urol 1989;141:190-1.
6. Johnson DE, Babaian RJ, von Eschenbach AC, Wishnow KI, Tenney D. Ketoconazole therapy for hormonally refractory metastatic prostate cancer. Urology 1988;31:132-4.
7. Trump DL, Havlin KH, Messing EM, Cummings KB, Lange PH, Jordan VC. High-dose ketoconazole in advanced hormone-refractory prostate cancer: endocrinologic and clinical effects. J Clin Oncol 1989;7:1093-8.
8. Oh WK. Secondary hormonal therapies in the treatment of prostate cancer. Urology 2002;60(3 Suppl 1):87-92.
9. Figg WD, Liu Y, Arlen P, Gulley J, Steinberg SM, Liewehr DJ. A randomized, phase II trial of ketoconazole plus alendronate versus ketoconazole alone in patients with androgen independent prostate cancer and bone metastases. J Urol 2005;173:790-6.
10. Scholz M, Jennrich R, Strum S, Brosman S, Johnson H, Lam R. Long-term outcome for men with androgen independent prostate cancer treated with detoconazole and hydrocortisone. J Urol 2005;173:1947-52.
11. Small EJ, Halabi S, Dawson NA, Stadler WM, Rini BI, Picus J, et al. Antiandrogen withdrawal alone or in combination with ketoconazole in androgen-independent prostate cancer patients: a phase III trial (CALGB 9583). J Clin Oncol 2004;22:1025-33.
12. Harris KA, Weinberg V, Bok RA, Kakefuda M, Small EJ. Low dose ketoconazole with replacement doses of hydrocortisone in patients with progressive androgen independent prostate cancer. J Urol 2002;168: 542-5.
13. Richie JP. Anti-androgens and other hormonal therapies for prostate cancer. Urology 1999;54(6A Suppl):15-8.
14. Wilkinson S, Chodak G. An evaluation of intermediate-dose ketoconazole in hormone refractory prostate cancer. Eur Urol 2004;45:581-4.
15. Bubley GJ, Carducci M, Dahut W, Dawson W, Daliani D, Eisenberger M, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. J Clin Oncol 1999;17:3461-7. Erratum in: J Clin Oncol 2000;18:2644.
16. Kelly WK, Scher HI, Mazumdar M, Vlamis V, Schwartz M, Fossa SD. Prostate-specific antigen as a measure of disease outcome in metastatic hormone-refractory prostate cancer. J Clin Oncol 1993;11:607-15.
17. Ryan CJ, Small EJ. Role of secondary hormonal therapy in the management of recurrent prostate cancer. Urology 2003;62(Suppl 1):87-94.
18. Millikan R, Baez L, Banerjee T, Wade J, Edwards K, Winn R, et al. Randomized phase 2 trial of ketoconazole and ketoconazole/doxorubicin in androgen independent prostate cancer. Urol Oncol 2001;6:111-5.
19. Walczak JR, Carducci MA; Eastern Cooperative Oncology Group E1899. Phase 3 randomized trial evaluating second-line hormonal therapy versus docetaxel-estramustine combination chemotherapy on progression-free survival in asymptomatic patients with a rising prostate-specific antigen level after hormonal therapy for prostate cancer: an Eastern Cooperative Oncology Group (E1899), Intergroup/Clinical Trials Support Unit study. Urology 2003;62(Suppl 1):141-6.