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EFFICACY OF KETOCONAZOLE IN HORMONE REFRACTORY PROSTATE CANCER PATIENTS

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Abstract:

Prostate cancer is a common malignancy among males, with the incidence steadily rising over the past years. Patients with small volume metastasis where early chemotherapy is not warranted, in patients with biochemical failure, and in patients who refuse chemotherapy, management remains controversial as there is no universally accepted treatment protocol. Ketoconazole is an antimycotic that inhibits cytochrome P450 enzymes that are required for the synthesis of androgens and other steroids. In addition, in-vitro studies have suggested some direct cytotoxic effects in prostate cancer cell lines. This study aims to describe our experience with ketoconazole treatment for hormone refractory prostate cancer (HRPC) at our centre. Retrospective chart review of HRPC patients given ketoconazole at a private oncology centre in Dhaka from 2005 - 2006 was done. Patients had histologically proven adenocarcinoma of the prostate with rising Prostate Specific Antigen (PSA) despite androgen deprivation therapy (ADT) with orchiectomy, LHRH agonist therapy and anti-androgens. Ketoconazole was given at 200 mg thrice daily. A total of 10 patients with HRPC was treated and evaluated for response and toxicity. Median age was 70 years old.4 (40%) of the 10 patients had a greater than 50% decrease of PSA values. Responses were seen in 66.66% (2/3) of patients with bone-only disease, 20 % (1/5) of patients with bone and soft tissue disease and 1 patient with PSA-only disease. Median duration of response was 6.75 months (range 2-14 months).There were no grade 3 or 4 toxicities. Overall, 5 (50%) patients had toxicity related to ketoconazole. Its good toxicity profile, low cost and ease of administration makes it a viable option to this group of patients specially in our country.

Keyword: *Prostate cancer, hormone refractory prostate cancer, ketoconazole*

Introduction

Prostate cancer is a common malignancy among males, with the incidence steadily rising over the past years. [1] With the advent of Prostate Specific Antigen (PSA), the incidence of prostate cancer is not on the rise, disease recurrence is also detected earlier. PSA detects a subset of patients with biochemical failure, defined as a rising PSA without objective evidence of metastasis after treatment for localized disease. Although some of these patients may be treated conservatively, there are patients treated early with androgen deprivation therapy (ADT) either due to the poor prognostic factors or due to patients' or even physicians' psychological refusal to accept conservative approach. Despite high response rate of 80-90% with ADT 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 with a survival advantage when used as first line treatment and is now the standard of care in metastatic hormone refractory prostate cancer (HRPC).[2] However, in patients with small volume metastasis where early chemotherapy is not warranted, in patients with biochemical failure, and 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 addition, in-vitro studies have suggested some direct cytotoxic effects in prostate cancer cell lines.[3,4] Studies of ketoconazole done during the pre-PSA era have shown response rates of 11-13% and disease stabilization in

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37-50% accompanied by marked palliation of pain.[5,6] Present studies using PSA as a marker of response showed a greater than 50% decrease in PSA in 40-63% of HRPC patients given high dose ketoconazole (HDK) at 400 mg thrice daily.[7-9] Median duration of response was 6 months.[8-10] A phase III trial using HDK with anti-androgen withdrawal (AAWD) vs AAWD alone reported PSA responses of 27% and 11%, respectively, with time to PSA progression 8.6 months in responders.[11] However, there were some grade 3-4 toxicities noted with all these studies including neurotoxicity, lassitude and hepatic toxicity. One approach to reduce toxicity is to use lower doses of ketoconazole. A phase II trial by Harris et al using low dose ketoconazole (LDK) 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.[12,13] This study aims to describe our experience with ketoconazole treatment for HRPC at our centre.

Materials & Methods

Retrospective chart review of HRPC patients given ketoconazole at a private oncology centre in Dhaka from 2005 - 2006 was done. Patients had histologically proven adenocarcinoma of the prostate with rising PSA despite ADT with orchiectomy, LHRH agonist therapy and anti-androgens.

Ketoconazole was given at 200 mg thrice daily. Replacement doses of oral hydrocortisone or prednisolone were given in four out of 10 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 pre-treatment level and confirmed by a second PSA value four or more weeks later. Endpoints were to determine response and duration of response. Secondary endpoint was to determine toxicity profile.

Results

A total of 10 patients with HRPC was treated and evaluable for response and toxicity. Median age was 70 years (range 57-85 years). Three had bone-only disease, five had bone and soft tissue disease, one had soft tissue-only disease and one had PSA-only disease. Median PSA was 354.5 ìg/ml (range 22.4-2500 ìg/ml) at the start of ketoconazole (Table-I).

Four (40%) of the 10 patients had a greater than 50% decrease of PSA values with ketoconazole. Responses were seen in 66.66% (2/3) of patients with bone-only disease, 20 % (1/5) of patients with bone and soft tissue disease and one patient with PSA-only disease. Median duration of response was 6.75 months (range 2-14 months). Median time to reach PSA nadir was 5.06 months (range 1.5-11 months) (Tabel-II). Two patients continue to exhibit response at the time of writing. Out of the 4 responders, ketoconazole was increased to 400 mg in one patient due to subsequent rise in PSA values after initial response and responded to ketoconazole 400 mg.

Ketoconazole was generally well-tolerated. There were no grade 3 or 4 toxicities. Overall, 5 (50%) patients had toxicity related to ketoconazole. 4 patients had grade 1 elevations in transaminases.

Table-I

Pretreatment Characteristics (n=10)

Age	
Median	70 years
Range	57-85 years
Extent of disease	
Bone only	3
Bone and soft tissue	5
Soft tissue only	1
PSA only	1
PSA at entry	
median	354.5 ug/ml
Range	22.4-2500 ug/ml

Table-II

Clinical outcomes on responders(n=10)

PSA > 50% decline	4(40%)
Bone only	2
Bone and soft tissue	1
PSA only	1
Time to PSA nadir	
Median	5.06 months
Range	1.5-11 months
Duration of response	
Median	6.75 months
Range	2-14 months
Adverse events	
Grade 1 transaminitis	4
Grade 2 transaminitis	1

Discussion

A 40 % PSA response was noted in this retrospective study of low dose ketoconazole in HRPC patients. This result is almost similar to that of Harris et al where a 46% PSA response was demonstrated.[12] Ketoconazole should be taken on an empty stomach as drug absorption is better with an acidic gastric environment. If possible, antacids, H_2 blockers or proton pump inhibitors should not be taken. These measures may not have been followed by patients resulting in suboptimal bioavailability of the drug.

The use of PSA as an endpoint is still a subject of debate at present. However, PSA has been well-documented as a surrogate marker of response. Changes in PSA may antedate changes in bone scans which may have a significant bearing in management.[14] A PSA response has also been correlated with improved median survival and time to treatment failure.[11,14-16]

Replacement doses of hydrocortisone or prednisolone were given to patients as ketoconazole is a potent inhibitor of adrenal steroid synthesis. Corticosteroids in itself exhibit anti-tumor effects by ACTH inhibition via negative feedback. This results to decreased androgen production in the adrenals. Hydrocortisone and prednisone have shown 16-22% PSA response while one study using dexamethasone has shown 61% PSA response.[17] There are no randomized trials to say which of the above steroids is most effective. In our study, steroids were given only in 50% of patients, hence, its use may have an additive effect on ketoconazole but our result of 40% PSA response demonstrates that ketoconazole accounts for most of the activity.

Toxicities were minimal in our study. Although 50% reported adverse effects, they were generally manageable and no one discontinued the drug. This is in contrast with the studies on high dose ketoconazole. where grade 3-4 toxicities were noted necessitating discontinuation of the drug.[9,10,18] No symptoms of adrenal insufficiency were seen in the patients who were not given steroids. This suggests that steroids may be omitted in patients with low dose ketoconazole but this should be further explored in a randomized clinical trial where steroid function is monitored.Limitations of this study include limited number of patients evaluated and 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 makes it a viable option to this group of patients specially in our country. Further studies are needed to explore this aspect of HRPC. We await the result of a study by the Eastern Cooperative Oncology Group (ECOG). ECOG 1899 is a phase III randomized trial evaluating second line hormonal therapy (ketoconazole/hydrocortisone) versus combination chemotherapy (docetaxel/estramustine) on progression free survival in HRPC patients. [19]

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