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Review article

Randomized phase 2 trial of ketoconazole and ketoconazole/doxorubicin in androgen independent prostate cancer

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Abstract

Eighty-nine patients with progressive prostate cancer despite suppression of testosterone and withdrawal of anti-androgens were studied. This was a relatively advanced population, with 63 of 89 having either osseous metastases (mets) beyond the axial skeleton or visceral mets. Patients were randomly assigned to receive either ketoconazole alone, or ketoconazole with weekly doxorubicin. All patients received replacement hydrocortisone. The primary endpoints were response and survival. Based on PSA reduction criteria ($\geqslant$ 80% maintained for at least 8 weeks), 14 of 45 patients (31%) in the single-agent ketoconazole arm responded. Sixteen of 44 patients (36%) in the combination ketoconazole/doxorubicin arm responded. There were no important differences between the two treatments in any outcome measure. The median overall survival for all patients was 12.5 months; median time to progression was 3.3 months. Toxicity was significant with both regimens, and more severe in the doxorubicin arm. Fully 20% of patients in each arm discontinued therapy due to intolerable side effects.Each of these regimens is toxic, and produced responses in fewer than half of treated patients. Although the observed median survival does compare favorably with reports from similar cohorts treated in the community, the potential benefit is only modest. In our view, neither of these regimens is sufficiently promising to justify phase 3 evaluation.

Keywords: Prostate; Ketoconazole; Doxorubicin; Randomized; Community; Phase II

1. Introduction

Hormone refractory prostate cancer continues to be a major therapeutic challenge and to claim more than 40,000 lives annually. Despite the increasing recognition that combination chemotherapy has clinically relevant anti-tumor activity [1,2], there is still no standard therapy for the thousands of men who will pass the benchmark of androgen independent progression this year. Recently, there has been renewed interest in the use of ketoconazole in this setting [3,4]. In fact, some recent reports suggest that ketoconazole is among the most active agents available, with high PSA-defined response rates reported [5,6]. Renewed interest in ketoconazole derives in part from the recognition that bioavailability is critically dependent on gastric acidity, which may account for some of the variability in previous reports using this agent. In addition, ketoconazole may exert effects beyond suppression of steroid hormone synthesis [7–9].

For several years, ketoconazole in combination with doxorubicin has been an integral part of our approach to advanced prostate cancer at the University of Texas M.D. Anderson Cancer Center [910]. We have used weekly doxorubicin in these studies in keeping with the observation that in general, chemotherapeutic agents have more impact in prostate cancer when they are given frequently in modest doses, as opposed to dosing at or near the MTD every 3 to 4

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weeks as is typical for more chemosensitive cancers [1]. Others have investigated ketoconazole in combination with oral cyclophosphamide [11].

So far, most reports of ketoconazole use in androgen independent prostate cancer (either alone or in combination) have come from referral centers, and the suitability of this treatment for the community setting is uncertain. In addition, we thought that it was of substantial interest to see if either (or both) of these regimens appeared sufficiently active to be tested in phase 3 evaluation. Accordingly, we have performed a randomized phase 2 trial of ketoconazole alone vs. ketoconazole/doxorubicin in community (CCOP) affiliates of the M. D. Anderson Cancer Center. The primary goals of this study were to define the response rates and toxicities observed with these regimens in the community setting. A randomized phase 2 design provides several advantages in this context. First, the impact of PSA testing continues to be reflected in significant stage migration in patients with prostate cancer, making comparison with historical benchmarks especially problematic. Second, selection of one regimen over another for further development is an important, well-established use of this design [12]. Finally, especially in the context of a common disease in which a two-arm trial does not seriously prolong accrual time, it is of interest to have some basis for recognizing large differences between therapies. We have previously used this design to conclude that neither 5-fluorouracil nor 5-fluorouracil in combination with interferon were promising [13] and that vinblastine in combination with estramustine was likely to be more active than vinblastine alone [14].

2. Materials and methods

2.1. Patients

Eligible patients had histological proof of adenocarcinoma, “castrate” testosterone levels (defined as $<$50 ng/dl for the purposes of this study), and evidence of androgen independent progression within the six months prior to registration. No prior exposure to the study agents was allowed. Patients had no more than one previous exposure to cytotoxic agents. Patients were off antiandrogens for at least 4 weeks or had progression since antiandrogen withdrawal. All patients had serum PSA greater than 4 ng/ml at entry. Adequate physiologic reserve was demonstrated by an estimated creatinine clearance of at least 35 ml/min; serum levels of hepatic transaminases less than twice the upper limit of normal; and no evidence of bifasicular block by electrocardiography (EKG). All patients had either a negative cardiac system review with a normal EKG, or a measured left ventricular ejection fraction of at least 45%.

Exclusion criteria included taking supraphysiologic doses of corticosteroids, active peptic ulcer disease or a requirement for antacid use, an active second malignancy or uncontrolled lesions within the central nervous system.

Patients were prospectively stratified according to extent of disease into four categories: local/regional only (i.e. normal bone scan at entry); bone disease limited to the axial skeleton; bone disease involving long bones; or visceral involvement. This stratification was done in order to help insure prognostic balance between the two groups; no sub-set analysis of these groups was planned or performed.

2.2. Treatment

All patients were treated with ketoconazole, 400 mg p.o. tid. Care was taken to instruct patients to take this apart from meals, either one hour before or two hours after eating. In addition, in order to insure an acidic gastric environment, patients were instructed to take the ketoconazole with 250 mg of ascorbic acid. In the ketoconazole/doxorubicin arm, patients were treated with ketoconazole as above, and then, starting with the second week, were given weekly doxorubicin, 20 mg/m^2 i.v., either as a brief “piggyback” or as a 24 h infusion, at the discretion of the treating physician. In the absence of toxicity, doxorubicin was continued to a cumulative dose of 400 mg/m^2. In general, therapy was continued until progression or “maximum benefit” as judged by the treating physician.

Patients unable to tolerate ketoconazole due to GI distress were offered sucralfate suspension. This was taken 1 h before or 2 h after a dose of ketoconazole. If symptoms persisted, then ketoconazole was reduced to 200 mg tid. All patients received hydrocortisone, 20 mg q AM and 10 mg q PM. This is necessary to avoid symptomatic corticosteroid deficiency at these adrenolytic doses of ketoconazole.

2.3. Criteria for response and progression

For patients without measurable disease, response was defined as a PSA decrease of at least 80% sustained for at least 8 weeks, with at least stable symptoms. In addition, patients with conventionally measurable disease were required to show at least 50% reduction in the product of the greatest dimension and its perpendicular. Progression was defined by any of the following events: 25% increase in PSA above the nadir level; new lesions by bone scan or other imaging modality; worsening symptoms attributed to prostate cancer. In order to avoid bias introduced by infrequent PSA measurements, all progression times were derived by linear interpolation of the PSA measurements on either side of the threshold for progression (i.e., 25% increase over PSA nadir). This procedure always provides a conservative estimate for the date of progression.

2.4. Statistical considerations

The historical response rate with ketoconazole is about 40%. According to the selection design of Simon et al. [12] a two arm randomized phase 2 trial with 37 patients per arm provides a 90% chance of correct selection if the true response rates are 40% and 55% respectively. Thus the accrual goal of 45 patients per arm provided ample power for correct selection. Although formal hypothesis testing was

not an objective of this small trial, large differences could certainly be detected. (This trial had an 80% power to reject a null hypothesis if the median survival was 9 months in one arm and 17 months in the other.) The primary end-points of the trial were response and survival. We also report time to progression (TTP). Although "response duration" is of interest, there is considerable uncertainty in defining both the time of "response" and the time of "progression." Thus, we report TTP (which is uncertain on only one end of the interval) stratified by response. We believe this provides the most objective and informative way to describe the durability of the observed responses.

3. Results

Between July 1995 and October 1996, 90 patients were registered from 22 CCOP affiliates. No patients were enrolled from the University of Texas M. D. Anderson Cancer Center. One patient was subsequently found to be ineligible due to concurrent therapy with strontium-89. All other patients are reported for response, survival and toxicity, irrespective of how much therapy they actually received (intent to treat analysis). Patient characteristics are summarized in Table 1.

As of this report (median follow-up of 3 years), all but one patient has progressed; 83 of 89 (92%) have died. In the ketoconazole only group, 14 of 45 (31%; 95% c.i. 18–47%) responded. The median survival was 12.5 months, with 7 patients (15%) surviving at 2 years. In the ketoconazole/doxorubicin group, 16 of 44 (36%; 95% c.i. 22–52%) responded. The median survival was 12.5 months, with 3 patients (7%) surviving at 2 years. Since rates of PSA decline of $\geqslant$50% are also commonly reported, we relate that 18 of 45 (40%) in the ketoconazole arm and 22 of 44 (50%) in the combination arm met this criterion. Only 14 (16%) of our patients had conventionally "measurable" disease at study entry. Of the twelve patients for whom follow-up imaging studies were obtained, 2 demonstrated a conventional PR, and both had PSA reduction of $>$80%. Of the other 10, there was only one patient with an 80% PSA reduction, but no objective response in his measurable disease—a 6 $\times$ 6 cm liver mass.

The median TTP for all patients was 3.3 months. TTP by response status is shown in Fig. 1. Of those patients who have died, all but two died of prostate cancer. Thus, overall survival is essentially identical to cause-specific survival in this cohort. Kaplan-Meir survival curves for the two cohorts are shown in Fig. 2. Extent of disease at study entry had a significant impact on outcome. As shown in Fig. 3, patients with involvement of long bones or viscera did significantly worse than patients with disease confined to the axial skeleton [15]. As is universally reported, patients demonstrating a major PSA response had a much better survival (Fig. 4).

Toxicity was significant, and dominated by gastrointestinal complaints such as bloating, nausea, heartburn and anorexia. One patient on the single agent ketoconazole arm had grade 4 hepatotoxicity requiring hospitalization; he had consumed 1 to 2 beers per day for several years, but was not known to have established liver disease. There was one death from myocardial infarction in each group. A striking finding in our study, in agreement with Mahler [16] and our previous anecdotal experience, but in contrast to the report of Small et al. [5], was the very high rate of patient withdrawal for intolerance of therapy. Overall toxicity results are summarized in Table 2. Although it is clear that many more grade 3 adverse events were observed in the combination arm, it is interesting that an equal number of patients (fully 20%) in each arm discontinued therapy for intolerable side effects.

All patients participating in this study were free to have any other treatment at the time of disease progression. Four patients on single agent ketoconazole were subsequently treated with ketoconazole/doxorubicin; all responded. Interestingly, five other patients were treated with mitoxantrone/prednisone following progression on single agent ketoconazole and none responded. Three patients initially treated on

Table 1
Patient characteristics at entry

Feature	KETO	KETO/DOX
Local/regional involvement	2	1
Axial skeleton only	11	12
Long bone involvement	25	23
Visceral involvement	7	8
Age at registration	70.9 yrs	70.1 yrs
(range)	(51–82)	(48–85)
Age at diagnosis	65.3 yrs	67.3 yrs
(range)	(47–78)	(47–81)
PSA at entry	98 mg/ml	200 ng/ml
(range)	(5–3,255)	(11–2,335)
Time, hormone therapy to registration	3.8 yrs	3.0 yrs
(range)	(0.5–9.3)	(0.3–11.3)

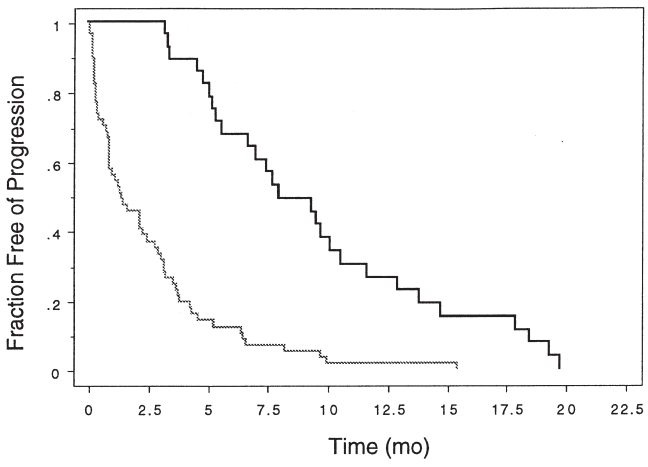

Fig. 1. Actuarial survival based on all-cause mortality. All eligible patients included. Kaplan-Meier estimates of TTP in non-responders (n=61; lower curve) and responders (n=28; upper curve).

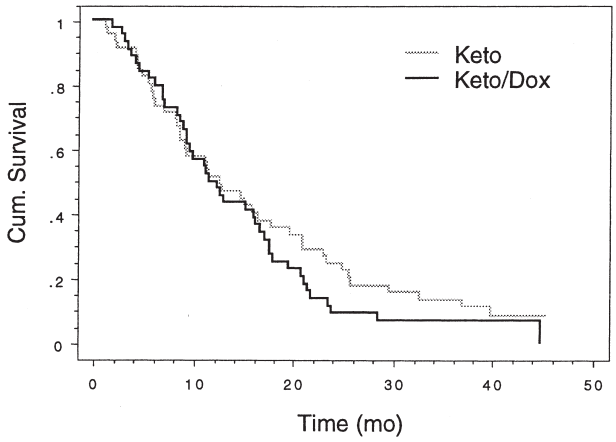

Fig. 2. Kaplan-Meier estimates of overall according to treatment. Keto=Ketoconazole; Dox=Doxorubicin.

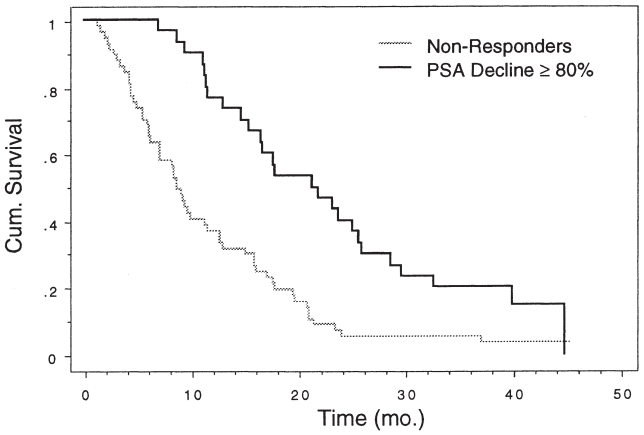

Fig. 4. Kaplan-Meier estimates of survival by response status.

the combination arm were subsequently treated with either single agent estramustine or mitoxantrone/prednisone; none responded.

Discussion

The optimal treatment of advanced prostate cancer is not known. Recent studies have confirmed a measurable, clinically relevant palliative impact of some therapies. It is becoming clear that "secondary" hormonal responses in advanced prostate cancer are not as rare as once believed. The recent report [17] of a 55% response rate and obvious clinical palliation achieved with dexamethasone is striking in this regard. Although physiologic replacement doses of hydrocortisone were given in this trial, it is unlikely that the observed effects were attributable to hydrocortisone. The available data on single-agent prednisone [18], does not suggest that the responses seen in this trial are associated with physiologic replacement doses of corticosteroids. The effect of dexamethasone seems to be a peculiar property of this agent given at the 0.75 mg bid dose. Remarkably however, there are no options for adrenal suppression that have a favorable toxicity profile. Exogenous glucocorticoids, ketoconazole, aminoglutethimide, mitotane, etc. are all fraught with considerable morbidity. With respect to more conventional cytotoxic therapy, many investigators have recently reported combination regimens in advanced prostate cancer. Although significant alteration of the natural history of the disease has not yet been convincingly demonstrated, meaningful symptom palliation by use of cytotoxic therapy is now widely recognized. In fact, the National Comprehensive Cancer Network guidelines [19] have endorsed two sequential trials of systemic cytotoxic therapy (including Sr-89 as an option in this category) as appropriate in the standard, palliative management of patients with androgen independent prostate cancer.

In our view, the present trial does confirm biologic activity of ketoconazole-based therapy, with many patients having significant PSA declines and clinically relevant periods of freedom from progression. Further, the median survival we observed in the community setting in a cohort with far-advanced, progressive disease compares favorably with the community experience recently disclosed for mitoxantrone/

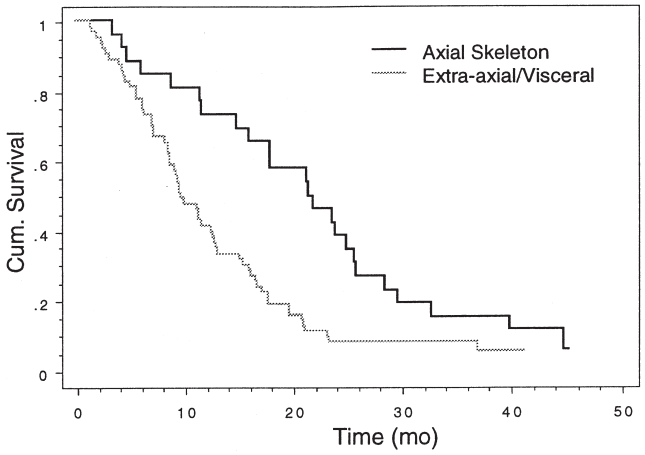

Fig. 3. Kaplan-Meier estimates of survival for all patients by extent of disease at entry. Patients with disease confined to axial skeleton (n=26) had a much better outcome than patients with extra-axial or visceral metastases (n=63).

Table 2
Summary of observed toxicities according to NCI Common Toxicity Criteria v. 2.0.

	KETO			KETO/DOX		
Grade	⩽2	3	4	⩽2	3	4
Anemia	8	0	0	15	3	1
Anorexia	2	1	0	7	1	0
Bilirubin increase	0	1	1	2	0	0
Diarrhea	5	2	0	10	0	0
Fatigue	3	1	0	10	4	0
Granulocytopenia	0	0	0	9	8	1
Nausea alone	14	2	0	22	3	1
Stomatitis	1	0	0	6	6	0
Thrombocytopenia	5	0	0	12	1	0
Vomiting	8	1	0	12	3	1

prednisone (median survival of 12.5 months vs. 7.8 months) [18]. Despite this, it is clear that a truly therapeutic threshold has not yet been crossed.

In conclusion, we found no evidence that either of these regimens is likely to substantially improve the survival of patients with androgen independent prostate cancer. However, the confirmation of a markedly better outcome in the setting of significant PSA declines, and many patients with symptom palliation, does confirm some biologic activity for this treatment, and suggests to us that further work on such regimens is reasonable. In our view, additional studies with novel combinations are more appropriate than taking either of these regimens on to phase 3 evaluation.

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References

[1] Millikan RE. Chemotherapy of advanced prostatic carcinoma. Sem Oncol 1999;25:185–91.
[2] Oh WK, Kantoff PW. Docetaxel (Taxotere)-based chemotherapy for hormone-refractory and locally advanced prostate cancer. Sem Oncol 1999;26:49–54.
[3] Jubelirer SJ, Hogan T. High dose ketoconazole for the treatment of hormone refractory metastatic prostate carcinoma: 16 cases and review of the literature. J Urol 1989;142:89–91.
[4] Muscato JJ, Ahmann TA, Johnson KM, Wilding W, Monaghan G, Schlossman DM. Optimal dosing of ketoconazole (KETO) and hydrocortisone (HC) leads to long responses in hormone refractory prostate cancer. Proc Annu Meet Am Soc Clin Oncol 1994;13:A701.
[5] Small EJ, Baron AD, Fippin L, Apodaca D. Ketoconazole retains activity in advanced prostate cancer patients with progression despite flutamide withdrawal. J Urol 1997;157:1204–7.
[6] Pavlick AC, Pecora AL, Scheuch J, et al. Treatment of hormone refractory prostate cancer with ketoconazole, hydrocortisone and cyclophosphamide. Proc Annu Meet Am Soc Clin Oncol 1996;15:A698.
[7] Eichenberger T, Trachtenberg J, Toor P, Keating A. Ketoconazole. A possible direct cytotoxic effect on prostate carcinoma cells. J Urol 1989;141:190–91.
[8] Siegsmund MJ, Cardarelli C, Aksentijevich I, Sugimoto Y, Pastan I, Gottesman MM. Ketoconazole effectively reverses multidrug resistance in highly resistant KB cells. J Urol 1994;151:485–91.
[9] Sella A, Kilbourn R, Amato R, et al. Phase II study of ketoconazole combined with weekly doxorubicin in patients with androgen-independent prostate cancer. J Clin Oncol 1994;12:683–88.
[10] Ellerhorst JA, Tu SM, Amato RJ, et al. Phase II trial of alternating weekly chemohormonal therapy for patients with androgen-independent prostate cancer. Clin Cancer Res 1997;3:2371–76.
[11] Maulard-Durdux C, Dufour B, Hennequin C, et al. Phase II study of the oral cyclophosphamide and oral etoposide combination in hormone-refractory prostate carcinoma patients. Cancer 1996;77:1144–48.
[12] Simon R, Wittes RE, Ellenberg SS. Randomized phase II clinical trials. Cancer Treat Reports 1985;69:1375–81.
[13] Daliani D, Eisenberg PD, Weems J, Lord R, Fueger R, Logothetis CJ. The results of a phase II randomized trial comparing 5-fluorouracil and 5-fluorouracil plus alpha-interferon. Observations on the design of clinical trials for androgen-independent prostate cancer. J Urol 1995;153:1587–91.
[14] Amato RJ, Logothetis CJ, Dexeus FH, Sella A, Kilbourn RG, Fitz K. Preliminary results of a phase II trial of estramustine (EMCYT) and vinblastine (VLB) for patients (pts) with progressive hormone refractory prostrate carcinoma (HRPC). Proc Amer Assoc Cancer Res 1991;32;A1111:186.
[15] Logothetis CJ, Hoosein NM, Hsieh JT. The clinical and biological study of androgen independent prostate cancer (AI PCa). Sem Oncol 1994;21:620–9.
[16] Mahler C, Verhelst J, Denis L. Ketoconazole and liarozole in the treatment of advanced prostatic cancer. Cancer 1993;71:1068–73.
[17] Storlie JA, Buckner JC, Wiseman GA, Burch PA, Hartmann LC, Richardson RL. Prostrate specific antigen levels and clinical response to low dose dexamethasone for hormone-refractory metastatic prostate carcinoma. Cancer 1995;76:96–100.
[18] Dowling AJ, Czaykowski PM, Krahn MD, Moore MJ, Tannock IF. Prostate specific antigen response to mitoxantrone and prednisone in patients with refractory prostate cancer. Prognostic factors and generalizability of a multicenter trial to clinical practice. J Urology 2000; 163:1481–5.
[19] Millikan RE, Logothetis C. Update of the NCCN guidelines for treatment of prostate cancer. Oncology 1997;11:180–93.