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# Phase II Study of Ketoconazole Plus Granulocyte-Macrophage Colony-Stimulating Factor for Prostate Cancer: Effect of Extent of Disease on Outcome

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**Purpose:** The efficacy of ketoconazole plus the immunostimulatory cytokine granulocyte-macrophage colony-stimulating factor was prospectively evaluated in patients with castration resistant prostate cancer with and without metastases.

**Materials and Methods:** Eligible patients had progressive castration resistant prostate cancer by consensus criteria and had received no prior immunotherapy, chemotherapy or ketoconazole. Patients received 400 mg ketoconazole orally 3 times daily, and 20 mg hydrocortisone orally each morning and 10 mg hydrocortisone orally each evening. Granulocyte-macrophage colony-stimulating factor ( $250 \mu\text{g}/\text{m}^2$ ) was administered subcutaneously on days 15 to 28 of each 28-day cycle. Progression was defined as disease progression or toxicity.

**Results:** A total of 49 patients were enrolled, including 37 with radiographically evident metastases and 12 with prostate specific antigen only disease. Median patient age was 68 years (range 52 to 84) and median prostate specific antigen was 23.1 ng/ml (range 5.4 to 306.5). Time to progression, which was the primary study end point, was 9.7 months for all patients. Ten of the 30 treatment failures showed radiographic progression and 6 were due to toxicity, while treatment failure in 14 of 30 patients (47%) consisted only of increasing prostate specific antigen. Median time to progression was 6.9 and 15.4 months in patients with and without metastases, respectively ( $p = 0.01$ ). Of 48 patients 36 (75%, 95% CI 60–86) experienced a 50% or greater decrease in prostate specific antigen. Four grade 4 events occurred that were unrelated to the study drug. Grade 3 events related to study therapy in more than 1 patient consisted of fatigue in 7 (14%).

**Conclusions:** Combined ketoconazole and granulocyte-macrophage colony-stimulating factor yields a high response rate and it is an option for patients with castration resistant prostate cancer. Time to progression in patients without metastases is significantly longer than in those without metastases.

*Keywords: prostate, prostatic neoplasms, ketoconazole, granulocyte-macrophage colony-stimulating factor, neoplasm metastasis*

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The emergence of castration resistance was a critical event in the natural history of prostate cancer. Although multiple secondary hormonal approaches have been studied for CRPC,<sup>1–3</sup> the duration of response to such therapies is relatively short.

The antifungal drug ketoconazole has been studied extensively for CRPC because of its ability to decrease levels of circulating adrenal androgens.<sup>4,5</sup> In a multicenter, randomized, phase III study of ketoconazole plus hydrocortisone 27% of patients experienced a 50% or greater decrease in PSA, although median TTP was only 4.6 months.<sup>6</sup>

GM-CSF, a hematopoietic growth factor that expands neutrophils and antigen presenting cells, has been studied in various clinical situations in prostate cancer. Consistent decreases in PSA have been noted in patients with metastatic CRPC<sup>7</sup> and in serological relapse after local therapy.<sup>8</sup> However, while GM-CSF appears to modulate PSA levels, to our knowledge the impact of this agent when combined with other agents with anti-prostate cancer efficacy is not known.

A trial of ketoconazole plus GM-CSF was performed based on the premise that adding GM-CSF to the presumed cytotoxic effects of ketoconazole would recruit dendritic cells in an environment in which some degree of cytolysis and antigen presentation was already present. The treatment cohort consisted of patients with CRPC with and without metastases based on the assumption that the disease state (metastatic vs nonmetastatic) would not impact the response proportion or TTP.

## MATERIALS AND METHODS

The study was approved by the Committee on Human Research, University of California-San Francisco, which was the only study site.

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Study received approval from the Committee on Human Research, University of California-San Francisco.

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TABLE 1. Patient characteristics

	Overall	Metastasis	No Metastasis
No. pts (%)	49	37 (76)	12 (24)
Median age (range)	68 (52–84)	68 (52–84)	69 (60–74)
Median ng/ml baseline PSA (range)	23 (5.4–306.5)	27 (5.4–306.5)	10 (5.5–91.6)
Median gm/dl hemoglobin (range)	14 (10.3–16.4)	14 (10.3–16.4)	13 (12.3–14.6)
Median IU/l alkaline phosphatase (range)	80 (38–750)	83 (38–750)	76 (49–98)
Median Gleason score (range)	7 (5–10)	7 (5–9)	8 (5–10)
No. opiate analgesia (%)	6 (12)	6 (16)	0

### Patient Population

Eligible patients included men with prostate cancer that had progressed despite androgen deprivation therapy, consisting of luteinizing hormone-releasing hormone agonist or orchiectomy. Patients were required to have disease progression according to consensus criteria.<sup>9</sup> Normal renal, hematological and liver function was required. No prior immunotherapy, ketoconazole or chemotherapy was allowed. Patients with only PSA evidence of disease were eligible, as were patients with positive imaging (bone scan or cross-sectional imaging of the abdomen and pelvis).

### Study Therapy

Therapy consisted of 400 mg ketoconazole orally 3 times daily plus 20 mg hydrocortisone in the morning and 10 mg hydrocortisone in the evening. All patients were counseled to ingest the medication on an empty stomach and avoid antacid medications. Ketoconazole is commercially available and it was provided to patients via prescription. All patients received 250  $\mu\text{g}/\text{m}^2$  GM-CSF (Leukine®) daily by self-administered subcutaneous injection for 14 days of every 28-day cycle. Baseline imaging consisted of bone scan, computerized tomography of the abdomen and pelvis, and chest x-ray. Patients with evidence of metastatic disease underwent repeat radiographic evaluation every 3 cycles. Patients with a negative initial radiographic evaluation were required to undergo repeat evaluation at disease progression. Disease progression was defined by consensus criteria, which required a 50% increase in PSA over the nadir and a minimum increase of 5 ng/ml or greater, or new lesions on bone scan.<sup>9</sup> Patients were evaluated monthly for toxicity, which was graded according to CTC, version 3.0. The concomitant use of statin lipid lowering drugs was not allowed, given the potential for interaction with ketoconazole. The protocol prohibited the initiation of GM-CSF if the total white blood count was 30,000/ $\text{mm}^3$  or greater at the start of the cycle.

### Statistical Considerations

The primary study end point was median TTP according to consensus criteria. With a 0.05 level of significance for a directional test with a power of 0.80 and an additional followup of 9 months after the completion of enrollment a sample size of 48 patients was required to detect a 50% increase in median time to PSA progression for the combination of ketoconazole plus GM-CSF for patients with CRPC compared with a historical control of approximately 5 months with ketoconazole alone, as observed in the mentioned phase III study.<sup>6</sup> The Kaplan-Meier product limit method was used to estimate the probability of TTP and

overall survival. Exploratory analyses were performed to compare the metastatic and nonmetastatic cohorts using the Fisher exact test for categorical variables, eg PSA response, and the nonparametric Mann-Whitney test for distributions, eg baseline PSA. Distributions of subsets for TTP or survival were compared using the log rank test.

## RESULTS

### Patient Characteristics

Between April 2004 and April 2006, 49 eligible patients were enrolled. Table 1 lists patient baseline characteristics. Median patient age was 68 years (range 52 to 84). Of the enrolled patients 47 had been treated with oral nonsteroidal antiandrogen, 6 had received greater than 1 prior antiandrogen, 5 had received high dose (150 mg or greater per day) bicalutamide and 3 each had received PC-SPES (Botanic Laboratories, Brea, California) and diethylstilbestrol.

Of the 49 patients enrolled 37 (76%) had metastatic disease, as defined by bone scan and/or computerized tomography, while 12 (24%) had no radiographic evidence of metastasis. Six of the 37 patients with metastasis (16% or 12% of the total) required opiate analgesics at the start of therapy. Baseline laboratory values were not different between patients with and without metastasis except PSA with lower baseline values in patients without metastasis (median 27.3 and 10.2 ng/ml,  $p = 0.05$ ). Median hemoglobin was 14 gm/dl (range 10.3 to 16.4), alkaline phosphatase was 80 IU/l (range 38 to 750) and Gleason score was 7 (range 5 to 10).

### Patient Disposition and Response to Therapy

Median followup in all patients was 15.0 months (range 2.3 to 30.1). Median followup in patients with and without metastasis was 12.7 (range 2.3 to 29.3) and 21.8 months (range 3.4 to 30.1,  $p = 0.03$ ). Eight patients remain on study therapy, including 5 and 3 with and without metastasis, respectively. Of the patients 30 discontinued therapy due to disease progression, including 26 and 4 with and without metastasis, respectively. Six patients discontinued study therapy due to toxicity and 5 withdrew by choice in response to mild toxicity that did not require study discontinuation (grade 1–2 chest pain from GM-CSF in 2) or for personal reasons (travel distance from the center). Four of the 5 patients who withdrew by choice did so at the time of a cycle that was beyond the median time to progression (cycles 10, 11, 15 and 16, respectively).

TTP, which was the primary study end point, was 9.7 months for all patients. Overall 36 of 48 patients (75%, 95% CI 60–86) who were evaluable for response achieved a PSA decrease of 50% or greater. The overall weighted TTP, ac-

TABLE 2. Outcomes in patients with CRPC with vs without metastasis

	PSA Only Disease		Metastasis		p Value
No. pts	12		37		
50% or Greater PSA decrease:					
No./total no. (%)	10/11	(91)	26/37	(70)	0.25
95% CI	59–100		53–84		
Median TTP (mos)	15.4		6.9		0.01
Median mos followup (range)	21.8 (3.4–30.1)		12.7 (2.3–29.3)		0.03
No. therapy (%):					
Continued	3	(25)	5	(14)	
Discontinued	9	(75)	32	(86)	
No. discontinuation reason (%):					
Progression PSA alone	3	(25)	17	(46)	
Objective progression	1	(8)	9	(24)	
Toxicity	2	(16)	4	(11)	
Withdrew consent	3	(25)	2	(5)	

counting for the fact that 75% of the patients enrolled in the study had metastases and 25% did not, was 9.0 months. Ten of the 30 treatment failures included radiographic progression, 6 were due to toxicity and treatment failure in 14 of 30 patients (47%) consisted only of increasing PSA. One patient experienced radiographic disease progression in the absence of serological progression. One patient withdrew consent within treatment month 1 and was excluded from response analysis. Two patients who discontinued therapy during month 2 due to toxicity (hyponatremia and atrial fibrillation in 1, and fatigue in 1) were considered unresponsive to treatment.

The proportion of patients with vs without metastasis who experienced a PSA decrease of 50% or greater as a function of disease state was 26 of 37 (70%, 95% CI 53–84) vs 10 of 11 (91%, 95% CI 59–100, Fisher's exact test  $p = 0.25$ ). Table 2 shows outcomes in the groups with and without metastasis. Of patients who discontinued study therapy

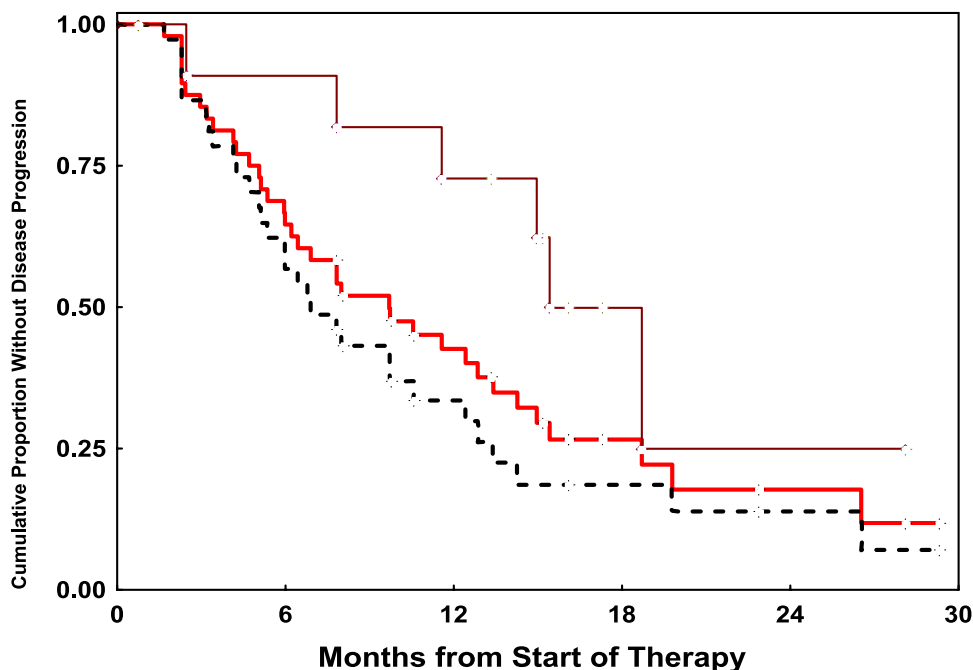
due to progressive disease or toxicity and were considered to show failure median TTP was 6.9 and 15.4 months for those with and without metastasis, respectively ( $p = 0.01$ , see figure). In the 26 patients with metastasis who experienced a response median TTP was 10.6 months, while it was 18.7 months in those with nonmetastatic disease who responded ( $p = 0.05$ ). A second analysis of the differences in outcome based on progression by PSA alone (which required an increase in PSA of 5 ng/ml above nadir PSA to define progression and excluded failures due to toxicity, in contrast to TTP defined by consensus criteria, in which radiographic progression could occur irrespective of the PSA value) demonstrated a TTP of 12.9 months in patients with metastasis, while it had not yet been attained in patients without metastasis ( $p = 0.04$ ).

### Toxicity

In 25 patients a total of 41 adverse events occurred (table 3). Four patients (8%) experienced CTC defined grade 4 events, including refractory hypertension, a ruptured duodenum, myocardial infarction and a skiing accident requiring hospitalization in 1 each. Of these events hypertension was classified as possibly related to ketoconazole/hydrocortisone. Grade 3 events consisted of fatigue in 7 cases (14%), urinary retention in 2 (4%), and syncope, dizziness, neuropathy, nausea, second malignancy (melanoma), rash, coagulopathy, noncardiac chest pain, bone pain, congestive heart failure, atrial fibrillation, hyponatremia, increased transaminase and urinary tract infection in 1 each (2%).

### DISCUSSION

Because prior studies have not conclusively demonstrated that a PSA decrease with GM-CSF leads to long-term disease control, the underlying hypothesis of the current study was that apoptotic tumor cells produced via a response to



TTP in all enrolled patients. Median TTP was 6.9 and 15.4 months in patients with (dashed line) and without (brown line) metastasis, respectively ( $p = 0.01$ ). Red line represents overall TTP curve.

TABLE 3. Toxicities by CTC, version 3 grade

CTC Grade (event)	No. Pts (%)
4:	
Hospitalization	1 (2)
Hypertension	1 (2)
Ruptured duodenum	1 (2)
Myocardial infarction	1 (2)
Total	4
3:	
Fatigue*	7 (14)
Urinary retention	2 (4)
Syncope	1 (2)
Dizziness	1 (2)
Neuropathy	1 (2)
Nausea*	1 (2)
Second malignancy (melanoma)	1 (2)
Rash*	1 (2)
Coagulopathy	1 (2)
Noncardiac chest pain*	1 (2)
Bone pain*	1 (2)
Congestive heart failure	1 (2)
Atrial fibrillation	1 (2)
Hyponatremia	1 (2)
Increased transaminase	1 (2)
Urinary tract infection	1 (2)
Total	25
2:	
Rash*	1 (2)
Hearing loss	1 (2)
Increased transaminase	1 (2)
Noncardiac chest pain*	1 (2)
Dysguesia	1 (2)
Azotemia	1 (2)
Bronchospasm	1 (2)
Total	10
1:	
Dyspnea	1 (2)
Bruising	1 (2)
Total	2

There were no grade 5 events.  
\* Deemed by investigator to be drug related.

ketoconazole would serve as antigens in an immune response stimulated by GM-CSF with the end result of this interaction being a longer duration of response than would be expected with ketoconazole alone.

The sample size of this study was calculated to detect a 50% increase in median time to PSA progression with ketoconazole plus GM-CSF for patients with CRPC compared with the observed median of 4.6 months with ketoconazole plus hydrocortisone alone in the phase III study performed by Cancer and Leukemia Group B.<sup>6</sup> In that study 84% of patients had metastatic disease, 29% required opiate analgesics for pain control at baseline and baseline PSA was 58 ng/ml, suggesting a greater burden of disease than in the current study cohort, in which 76% of patients had metastasis, 12% required opiate analgesic and median PSA was 23 ng/ml. Based on a comparison of TTPs in these 2 studies the observed overall time to progression of 9.7 months represents a greater than 50% improvement in outcomes against this historical control and the underlying statistical goal was met. Furthermore, the weighted TTP of 9.0 months, which corrected for the fact that 75% of patients had metastatic disease, is also above this number. Finally, the 6.9-month TTP observed in patients with metastasis was 50% longer than the 4.6 months in the phase III study.

Because comparisons of single center, phase II results to historical, multicenter, phase III data must be made cau-

tiously, it is important to point out that the current data compare favorably to those in the single center, phase II studies of ketoconazole done at our institution, in which 30 of 48 patients (62.5%) experienced a 50% or greater decrease in PSA. Despite this, the magnitude to which this combination may be an improvement over ketoconazole alone is not great enough to prioritize this combination over other strategies in development for CRPC.

### The Role of GM-CSF in CRPC

A major limiting factor in the development of combination based immunotherapies has been the lack of reliable biomarkers/surrogate markers for a tumor specific immune response. Nonspecific markers, such as pre-therapy and post-therapy levels of activated T cells, have been measured in patients treated with dendritic cell vaccinations<sup>10</sup> and the presence of tumor reactive antibodies in response to GM-CSF transduced cellular vaccines has been described.<sup>11</sup> In these reports vaccination was associated with increases in T-cell activation and the presence of tumor specific antibodies on Western blot. Despite supporting the hypothesis that these therapies cause immune activation, no correlation with clinical responses, TTP or other hard end points such as survival has been made. The current study did not include the measurement of putative markers of immune function. The development of a tumor specific method of immune monitoring that reliably correlates with clinical outcome may greatly accelerate the development of combination immune strategies.

The combined effects of stage migration in prostate cancer and the routine use of androgen deprivation therapy for patients with serological relapse have resulted in the population of patients with CRPC growing to include a substantial proportion without metastasis. In light of this fact a post hoc and exploratory analysis of patient outcomes based on disease extent at the start of therapy was performed. Patients with metastatic disease enrolled on this trial may reflect a typical contemporary cohort of patients initiating a secondary hormonal therapy in that, despite metastasis, they were largely free of end organ damage or poor risk features, eg median hemoglobin and alkaline phosphatase were within normal limits.

A total of 12 patients with nonmetastatic, castration resistant prostate cancer and 37 with metastasis were enrolled in the study. Outcome analysis comparing these 2 groups showed that, although there was no statistical difference in the proportion of patients who achieved a PSA decrease of 50% or greater, TTP (defined by PSA or objectively) in those without metastasis was substantially longer than in those with metastasis.

Although this study was not designed to directly compare these 2 patient populations, it may be the first to compare outcomes in patients with androgen independent prostate cancer who were treated with a single therapy specifically based on the distinguishing characteristic of the presence or absence of metastases. Furthermore, the observation that patients with nonmetastatic disease experienced significantly longer TTP than those with metastasis suggests that treatment resistance may be a function of tumor volume. These observations are limited by the relatively small sample size but they support the consideration of stratification

by tumor volume or extent in future studies of secondary hormonal therapies and immunotherapies. All comparisons by disease subset are exploratory, so that any probability value should be interpreted with caution and would be used to identify future investigations.

Another limitation of this analysis is the reliance on PSA as a determinant of TTP in patients with nonmetastatic disease. Differences in TTP may be accounted for by the consensus criteria requirement that the PSA must increase by 5 ng/ml above its nadir value, coupled with low baseline PSA in the nonmetastatic CRPC group (median 10.2 ng/ml). Therefore, the current analysis includes a calculation of TTP based only on the PSA increase as well as a calculation of TTP based on all factors, such as objective progression, toxicity and withdrawal of consent (see figure). These 2 analyses demonstrated a statistically significant difference in outcome between these 2 populations and suggest that this difference may not simply be an artifact of the consensus criteria for progression. Nevertheless, this potential for confounding the outcome analysis, if validated, could potentially form the basis for advocating that disease progression in patients without metastasis should be defined only by the development of metastatic disease. Defining progression in patients with nonmetastatic prostate cancer only by the development of metastatic disease is controversial and it is not currently the standard approach for end point determination in clinical trials. In the face of increasing PSA it is not recommended that patients should remain on a therapy such as the combination in this study until such time as metastasis develops.

Finally, no definitive additive toxicity to the combination of ketoconazole, hydrocortisone and GM-CSF was observed. Fatigue is a possible overlapping toxicity of ketoconazole plus GM-CSF and 7 cases of grade 3 fatigue were observed with this therapy. Two cases of noncardiac chest pain (grades 3 and 2 in 1 each) were also observed during the period of GM-CSF administration, potentially the result of sternal marrow expansion.

Approximately 10% of patients withdrew from study therapy by choice, of whom several did so despite responding to study therapy for a period longer than the median for the study. This may have been for reasons relative to study performance, eg monthly visits and the cost of travel to the study site, or for other personal reasons. However, this problem could potentially be avoided with treatment breaks, provided that patients continued to be monitored closely.

## CONCLUSIONS

These data suggest that the combination of ketoconazole/hydrocortisone and GM-CSF may lead to an improvement in TTP compared to that of ketoconazole alone. The mechanisms through which GM-CSF may potentiate ketoconazole are unclear, although GM-CSF may enhance the presentation of antigens derived from dying prostate cancer cells and induce a subsequent immune response. Furthermore, these data suggest that patients with a lower disease burden (nonmetastatic CRPC) experience longer TTP than those with a greater disease burden (metastasis) at study baseline despite the absence of an obvious difference in response proportion, suggesting that outcomes in such patients should be analyzed separately.

## ACKNOWLEDGEMENTS

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### Abbreviations and Acronyms

CRPC	=	castration resistant prostate cancer
CTC	=	Common Toxicity Criteria
GM-CSF	=	granulocyte-macrophage colony-stimulating factor
PSA	=	prostate specific antigen
TTP	=	time to progression

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**EDITORIAL COMMENT**

Since the pioneering studies of Dranoff et al in 1993 using GM-CSF transduced irradiated tumor cells as tumor vaccines,<sup>1</sup> the promise of using GM-CSF as an anticancer agent has tantalized the field of oncology. Small et al recognized that GM-CSF monotherapy may have antitumor effects in prostate cancer and in 1999 they reported provocative data indicating that GM-CSF alone could favorably modulate serum PSA in a subset of patients with advanced disease (reference 7 in article). The question then arises of whether GM-CSF adds in a significant way to current therapies with regard to improved clinical outcomes in prostate cancer? This question remains unanswered and it requires adequately powered, randomized trials using clinically relevant end points. Comparison between nonrandomized studies of

prostate cancer is particularly problematic. Current randomized studies are under way using GM-CSF transduced cellular vaccines and GM-CSF alone. We look forward to understanding more about the efficacy of this fascinating cytokine.

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