Phase II Study of Mitoxantrone and Ketoconazole for Hormone-Refractory Prostate Cancer

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BACKGROUND. Doxorubicin plus ketoconazole has exhibited significant activity in patients with advanced prostate cancer. However, overall and cardiac-specific toxicity was reported to be high. Mitoxantrone has activity similar to that of doxorubicin, is less cardiotoxic, and is widely used to treat prostate cancer. The current study sought to evaluate the toxicity and activity of mitoxantrone plus ketoconazole in a cohort of patients with hormone-refractory prostate cancer.

METHODS. Progression after medical or surgical castration and, for those patients receiving antiandrogens, progression after withdrawal was required, as was objective evidence of metastasis, castrate levels of testosterone, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and intact cardiac function. After enrollment onto a multicenter local consortium study, subjects were treated with mitoxantrone at a dose of 12 mg/m2 intravenously every 3 weeks plus continuous oral ketoconazole at a dose of 400 mg 3 times daily and ascorbic acid at a dose of 250 mg. Replacement doses of hydrocortisone were given.

RESULTS. For 40 enrolled subjects, the median prostate-specific antigen and ECOG performance status were 68 and 1, respectively, 53% had Gleason scores of 8 to 10, and all had metastasis. Predominant Grade 3/4 toxicities were: neutropenia in 13%, neutropenic fever in 10%, and anemia in 13%. Of 37 evaluable patients, 8% achieved a complete remission (CR) and 62% achieved a partial remission (PR), for a CR plus PR rate of 70%. For soft tissue and bone disease, overall response rates were 13% and 8%, respectively. The median progression-free survival and overall survival were 10 months and 18 months, respectively.

CONCLUSIONS. Mitoxantrone plus ketoconazole is well tolerated, is active in hormone-refractory prostate cancer, and should be studied further.

KEYWORDS: prostate cancer, chemotherapy, metastasis, hormone refractory, Phase II.

Prostate cancer was expected to be diagnosed in approximately 232,090 men in the U.S. in 2005, and will result in death in approximately 30,350.1 Treatment options for metastatic prostate cancer remain limited, with disease progression being inevitable after initial hormone therapy.2 Once hormones have failed, combination chemotherapy is typically employed. A variety of taxane-based regimens have been tested in hormone-refractory prostate cancer, yielding response rates between 38% to 69%,3-12 or 48% to 50% when tested in multicenter trials.9,10 As responses to taxane-based regimens have appeared to exceed those typically associated with mitoxantrone plus prednisone, taxane-based therapy has been widely used in the community, typically as a first-line therapy. Two recent Phase III trials have compared docetaxel-based therapies with mitoxantrone plus prednisone, and both have demonstrated the superiority of docetaxel,
in terms of response and survival. Therefore, increased use of taxane-based regimens as initial therapy is expected. Alternatives that are nontaxane-based and have comparable activities do not exist.

At a time when nontaxane-based regimens were associated with response rates of 30% to 40%, Sella et al. reported that the combination of doxorubicin plus ketoconazole was associated with a response rate of 55% in a hormone-refractory cohort. In addition, objective responses were observed in 7 of 12 patients (58%) with measurable soft tissue disease. However, toxicity was high, with 45% of patients requiring hospitalization for treatment-related complications, 29% experiencing Grade 3/4 neutropenia, and 5% experiencing sudden cardiac death.

Single-agent ketoconazole has been shown in a number of studies to have activity in prostate cancer. Whereas the mechanism(s) by which ketoconazole exerts anticancer activity is not clear, inhibition of adrenal androgen synthesis, as well as nonhormone-dependent effects, have both been implicated. In a cohort of patients with hormone-refractory prostate cancer, responses to single-agent ketoconazole ranged from 11% to 65%.

Mitoxantrone has a planar polycyclic aromatic ring structure, similar to that of doxorubicin and other anthracyclines, and therefore can intercalate into DNA in a similar fashion and has a similar spectrum of activity, but does not lead to the production of quinone-type free radicals, which are believed to be responsible for cardiac toxicity, and has less cardiac toxicity than doxorubicin. Mitoxantrone has been widely used, in combination with prednisone, for the treatment of hormone-refractory prostate cancer. Because mitoxantrone has a spectrum of activity similar to that of doxorubicin, but is less toxic, it was hypothesized that mitoxantrone plus ketoconazole would be active in men with hormone-refractory prostate cancer, and would be tolerable in an older cohort. The current study was designed to test this hypothesis.

MATERIALS AND METHODS

Patient Eligibility
Subjects were entered into an Institutional Review Board-approved protocol. Participating institutions constituted a local consortium and included Ingalls, Silver Cross, Munster Community, and Cook County Hospitals, as well as the Northwestern University-associated hospitals, Northwestern Memorial Hospital, and Jessie Brown Veterans Administration Medical Center. Subjects were eligible for study if they had histologically confirmed adenocarcinoma of the prostate, objective evidence of metastases (as measured by bone scan, computed tomography [CT], and/or physical examination), had disease progression after hormonal therapy, and had castrate levels of testosterone. Those whose only evidence of disease progression was prostate-specific antigen (PSA) elevation must have had prior objective evidence of metastasis. Participants must have been off all forms of active therapy for at least 1 month before study entry (exclusive of luteinizing hormone-releasing hormone agonist treatment, which was continued). Prior therapy with either mitoxantrone or ketoconazole was not allowed. Those receiving androgen receptor-blocking agents must have had confirmed disease progression after withdrawal.

Additional requirements included: an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, a life expectancy >3 months, a baseline cardiac ejection fraction of ≥55% (measured by either echocardiogram or multiple gated acquisition [MUGA] scan), and intact liver (bilirubin ≤1.5 mg/dL, transaminases ≤4 times the upper limit of normal), bone marrow (platelet count ≥100,000 per mm$^3$ and an absolute neutrophil count >1500 per mm$^3$) and renal (creatinine ≤2.5 mg/dL) function. Patients with active peptic ulcer disease or clinically significant heart disease were excluded. No concurrent use of proton pump inhibitors, H2 blockers, or antacids was permitted. People who were taking terfenadine or astemizole also were excluded.

Evaluations
Pretreatment evaluation included a medical history, physical examination, serum PSA level, serum testosterone level, complete blood count (CBC) with differential, electrolytes, liver function tests, an electrocardiogram, and a MUGA scan (or echocardiogram). Additional studies to define the extent of disease consisted of a CT scan of the abdomen and pelvis, a bone scan, a chest radiograph, and additional radiographic studies as clinically indicated. All participants provided both written and verbal informed consent.

While on study, subjects were followed with a weekly CBC and differential. History and physical examination, PSA, and serum electrolytes were repeated before each cycle. Individuals were completely restaged after every 3 cycles. For those in whom mitoxantrone was discontinued because continued treatment would exceed a cumulative dose of 140 mg/m$^2$ and were being maintained on ketoconazole only, history and physical examination, PSA, CBC with differential, and serum electrolytes were repeated monthly, whereas restaging studies were repeated every 3 months. Toxicity was assessed and scored at each scheduled clinic visit, or sooner if clinically indicated.
using the National Cancer Institute Common Toxicity Criteria (version 2.0).

Response Criteria
PSA Working Group consensus criteria were used to define response and progression for PSA, whereas non-PSA responses were defined as previously described. Specifically, a complete response (CR) required resolution of all clinical and radiographic evidence of disease and normalization of PSA for a duration of at least 6 weeks (2 cycles of therapy). A partial response (PR) required a >50 percent reduction in the sum of the products of the perpendicular dimensions of all soft tissue lesions, a decline in baseline PSA of >50% (maintained for at least 1 month), or the resolution of ≥1 lesions on bone scan, without the appearance of new lesions. Progressive disease (PD) was scored if there was a >25% increase in the sum of the products of the perpendicular dimensions of all measurable soft tissue lesions, the appearance of new soft tissue or bone lesions, or if there was a >50% increase in PSA from nadir value. To be scored PD based on PSA criteria alone, a confirmatory PSA was required 2 weeks after the initial PSA that was >50% over the nadir value. Once confirmed, the time of the first PSA value that was 50% elevated was used as the time of progression. Patients who experienced a decline in ECOG performance status, the onset of intractable pain, renal obstruction, or spinal cord compression due to prostate cancer were also considered to have PD. Patients who had improvement in ≥1 parameter while meeting the criteria for PD by another parameter were scored as having PD. Patients who did not meet the criteria for PR and did not experience PD were scored as having stable disease (SD).

Treatment
Treatment consisted of mitoxantrone at a dose of 12 mg/m² given intravenously every 3 weeks, up to a maximum cumulative dose of 140 mg/m². Concomitant with mitoxantrone, the following oral drugs were administered on a continuous basis: ketoconazole at a dose of 400 mg 3 times daily (either 1 hour before, or 2 hours after meals), ascorbic acid at a dose of 250 mg given 3 times daily (given with ketoconazole), and replacement doses of hydrocortisone (20 mg in the morning and 10 mg in the evening). Treatment was discontinued in the face of PD and/or for Grade 3/4 nonhematologic toxicity. Individuals who received maximum cumulative doses of mitoxantrone, but had not experienced PD, continued to receive ketoconazole, ascorbic acid, and replacement doses of hydrocortisone.

If on the day of treatment platelets were below

100,000/mm³, granulocytes were below 1000/mm³, or ≥Grade 3 toxicity was present, treatment was held for 1 week. Treatment could be held for up to 2 weeks and if by that time counts did not recover, or toxicity decreased to below Grade 3, no further mitoxantrone was administered. For those experiencing recovery, and for those who experienced Grade 3 nonhematologic toxicity during the cycle, subsequent doses of mitoxantrone were reduced by 20%. Ketoconazole was held for toxicity of ≥Grade 3, and was reinitiated with a one-third dose reduction once toxicity decreased to below Grade 2. For either drug, if toxicity persisted after 2 dose reductions, or if at any time the patient developed Grade 4 nonhematologic toxicity, treatment was withdrawn.

Statistical Methods
All patients entered into the study were formally registered and all registered patients were included in the final data analysis. To ensure the accuracy of data, a subset of charts was periodically reviewed by a dedicated independent Quality Control Manager according to guidelines established under the Northwestern University Data Safety and Monitoring Plan, which has been reviewed and approved by the National Cancer Institute.

The study was designed as a Phase II trial. Based on previous results of the use of doxorubicin plus ketoconazole, a response rate of 40% for the current study was considered to be too low to be of further interest. A scheme for the optimal 2-stage design of a Phase II trial is presented by Simon. Using the Simon method, 18 patients would be enrolled initially. If ≤7 responses were achieved among the first 18 patients, the trial would be terminated. Otherwise, up to an additional 28 patients would be entered, for a total of 46. Among these 46 patients the regimen would not be recommended for further study if ≤22 total responses were observed. The probability of early termination of this study if the true response rate was 40% would be .56. The type 2 and type 1 error rates were both set at 10%.

Because of the 2-stage design, determination of the 2-sided confidence limits for the proportion with SD or response was determined by a method taking this design into consideration. Survival and time to PD were calculated from on-study date until date of progression, death, or last follow-up. The Kaplan-Meier method was used to calculate the probability of survival or progression-free survival (PFS) as a function of time.
RESULTS

Patient Characteristics

Between March 1998 and May 2002, 40 patients were enrolled in the study. The median age of participants was 71 years (range, 50-85 years), the median ECOG performance status was 1 (range, 0-2), and the median PSA at baseline was 68 ng/mL (range, 18-1400 ng/mL) (Table 1). Fifty-three percent of patients had Gleason scores between 8 and 10, osseous disease was present in 85%, and 40% had soft tissue metastasis. All participants had objective evidence of metastasis, all had failed primary hormone therapy, all had castrate levels of testosterone, and 50% had received ≥1 additional systemic treatment regimens after failing primary hormonal therapy. Of the 2 patients who had received prior chemotherapy, it was taxane-based in both instances.

A total of 266 cycles of mitoxantrone were administered. The average number of cycles per subject was 7 (range, 0-11 cycles). The mean dose of mitoxantrone administered for the first cycle was 11 mg/m² (range, 0-12 mg/m²).

Toxicity

Toxicity data were available for 31 patients (Table 2). The predominant Grade 3/4 toxicity associated with treatment was bone marrow suppression, with 13% of individuals experiencing neutropenia and 10% neutropenic fever. Other Grade 3/4 toxicities were less common and of unclear relation to treatment. Two
patients had atrial dysrhythmia, 1 had syncope, and 1 discontinued treatment when he developed idiopathic thrombocytopenia purpura. Of lower-grade toxicities, edema was relatively common, but there were no episodes of congestive heart failure reported. Nausea/vomiting was associated with ketoconazole administration and was noted in 52%, was primarily Grade 1, and was generally responsive to treatment with antiemetics. Pain, anemia, and fatigue were also common.

Response and Survival
Of 40 patients enrolled, 37 were evaluable for response. One person refused therapy after being registered for the study, 1 had a massive stroke after 2 cycles and died shortly thereafter, and 1 person withdrew from study after 1 cycle because of gastrointestinal bleeding (the latter 2 in the face of normal platelets). There was no evidence of PD in any of these 3 cases.

Three patients (8%) achieved CR and 23 patients (62%) achieved a PR, giving a CR plus PR rate of 70%. For those with Gleason scores of 8, 9, and 10 disease, the CR, PR, and overall response rates were 10%, 70%, and 80%, respectively. All 3 of those patients achieving CR had pretreatment measurable soft tissue metastases, as well as elevated PSA, whereas 2 patients also had bone metastases. Four patients (11%) in the study had SD. Seven patients (19%) had PD. The overall response rate for bone disease was 8% (all CRs), whereas that for soft tissue was 13%. The median PFS and overall survival was 10 months and 18 months, respectively (Fig. 1).

DISCUSSION
The therapeutic options for men with hormone-refractory prostate cancer are limited. Because the combination of doxorubicin plus ketoconazole has been reported to have high activity, but high toxicity, and because mitoxantrone has a similar activity spectrum to doxorubicin, it was hypothesized that mitoxantrone plus ketoconazole would have high activity and low toxicity in a cohort with hormone-refractory prostate cancer. Findings from the current study directly support this hypothesis.

It is important to note that high response rates were attained even though a high proportion of participants had high-grade prostate cancer (i.e., a Gleason score of 8-10). A high Gleason score is known to be a poor prognostic indicator for individuals with metastatic disease.31 Because the goal of 22 responding patients was reached well before the planned maximum cap of 46, the study was terminated at 37 evaluable patients. If accrual had continued up to 46 patients, the worst-case scenario (no additional responses) and best-case scenario would have given overall response rates of 57% and 76%, respectively. Given the nature of the cohort, interest in further investigation would still remain even under the worst-case scenario. Although the current study represents a single report, the findings of which should be confirmed separately, it is important to note that it is in fact a multiinstitution study in which 5 separate institutions and 6 separate hospital systems participated.

Both ketoconazole and mitoxantrone have activity in prostate cancer. Mitoxantrone, even when combined with steroids, is reported to have low activity in prostate cancer.9,10,25,32 Ketoconazole has been exten-
sively evaluated in patients with advanced prostate cancer, with widely varying response rates.\textsuperscript{14–20,33,34} In more recent trials,\textsuperscript{16–20} in which PSA was used as an endpoint, response rates were higher, and ranged from 27% to 63%. Whereas the 63% response rate noted in 1 previous study\textsuperscript{16} approximates the 70% response rate seen in the current study, the same investigators recently reported a response rate of 27% in a trial that targeted a cohort of patients at an early stage of hormone independence.\textsuperscript{19} Higher response rates in an earlier cohort would have been expected. Again, it is also important to note that relatively high response rates were observed in the current study, despite the fact that a high percentage of participants had high-grade disease. Therefore, although the combination of mitoxantrone plus ketoconazole needs to be studied further, existing data support the notion that there is an added benefit to combining these 2 agents. It also should be noted that doxorubicin has an activity spectrum similar to that of doxorubicin and can be well tolerated and active in hormone-refractory prostate cancer,\textsuperscript{35,36} and therefore also may be suitable in combination with ketoconazole.

To our knowledge, until recently, no regimen had been shown to improve survival in men with hormone-refractory prostate cancer. Two recent reports demonstrate that docetaxel-based regimens improve survival, at least as compared with mitoxantrone plus prednisone (MP). Tannock et al.\textsuperscript{10} demonstrated that docetaxel plus prednisone gave superior responses and longer survival than did MP. Petrylak et al.\textsuperscript{9} reported a similar superiority with docetaxel plus estramustine. Before these reports, taxane-based regimens were widely used for hormone-refractory prostate cancer, even as first-line therapy.\textsuperscript{3–12} The use of taxane-based regimens is now expected to increase significantly. The results of the current study demonstrate that mitoxantrone plus ketoconazole has activity that appears to be similar to that of taxane-based regimens.

The combination of mitoxantrone plus ketoconazole is a well-tolerated regimen with significant activity for men with histologically aggressive, hormone-refractory prostate cancer. This combination warrants further study in men with prostate cancer. In particular, its activity in a hormone-refractory cohort should be independently confirmed.

REFERENCES


