A Phase II Study of High-Dose Tamoxifen in Patients with Hormone-refractory Prostate Cancer

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ABSTRACT

Micromolar concentrations of tamoxifen inhibit the activity of protein kinase C and were recently shown to inhibit prostate cancer cell growth in preclinical studies. Because micromolar concentrations can be attained with high-dose therapy, the clinical activity of high-dose tamoxifen was evaluated in patients with metastatic adenocarcinoma of the prostate. Between December 1993 and February 1997, 30 patients with hormone-refractory metastatic adenocarcinoma of the prostate were continuously administered tamoxifen at 160 mg/m²/day. Therapy was continued until disease progression. All study patients had failed prior treatment with combined androgen blockade, had castrate levels of testosterone, and were heavily pretreated, having received a median of three prior regimens. The average steady-state plasma concentration of tamoxifen was 2.96 ± 1.32 μM (mean ± SD). Grade 3 neurotoxicity was observed in 29% of patients and was rapidly reversible and readily managed with dose modification. Otherwise, grade 3 toxicities were rare. One partial response (80% decline in prostate-specific antigen) was observed (3.3%), whereas disease stabilization was observed in six patients (20%), for a combined partial response/stable disease response rate of 23%. Median time to progression was 2.1 months, and median survival time was 10.5 months. High-dose tamoxifen therapy was well tolerated and associated with micromolar concentrations of tamoxifen in human plasma, and it demonstrated activity, albeit limited, in a heavily pretreated patient cohort with hormone-refractory prostate cancer. These findings suggest that further investigation of the role of protein kinase C modulation in prostate cancer is warranted.

INTRODUCTION

This year in the United States, prostate cancer will be diagnosed in ~179,300 men and will result in death in ~37,000 men (1). However, treatment options for metastatic prostate cancer remain limited, with disease progression being inevitable after initial hormone therapy (2). Despite extensive research using a variety of agents, no survival benefit has been definitively demonstrated for the treatment of hormone-refractory disease (3, 4).

The development of agents that target processes that are relatively unique to prostate cancer is a logical approach to the development of more effective therapies (5). Recent advances have served to elucidate the molecular mechanisms underlying prostate cancer carcinogenesis and to guide the development of targeted therapy. Such an approach is currently being pursued by a number of investigators, with promising initial results (5–12). These approaches include targeting biochemical sites within the prostate cell nucleus, immunologically based methods, antiangiogenesis approaches, growth factor modulation, and antimetastatic approaches (5–10).

It has recently been shown that the estrogen agonist/antagonist, tamoxifen (1-[p-dimethylaminoethoxyphenyl]-1,2-di-phenyl-1-butene), inhibits the growth of prostate cancer cells in preclinical studies (9). Growth inhibition was not dependent upon estrogenic activity. It was, however, associated with inhibition of PKCβ (a known effect of tamoxifen), and direct activation of the TGF-β signaling pathway, including induction of the cell cycle-inhibitory protein, p21(rodent/cell) (9, 13, 14). TGF-β plays an important role in regulating prostate cell growth; however, prostate cancer cells appear to lose their growth-inhibitory response to TGF-β during the process of carcinogenesis (15–22). Whereas growth inhibition was only observed with tamoxifen concentrations exceeding 1 μM, prior studies have shown that micromolar concentrations can readily be attained in humans with high-dose tamoxifen therapy (23–25). To determine whether high-dose tamoxifen therapy had activity in prostate cancer, we initiated a Phase II clinical trial in patients with hormone-refractory prostate cancer.

PATIENTS AND METHODS

Patient Eligibility. Between December 1993 and February 1997, 34 patients were entered onto clinical protocol NCI

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93-C-0044, after review and approval by the Institutional Review Board of the National Cancer Institute. Pretreatment evaluation included history and physical examination, serum PSA level (Abbott Laboratories, Abbott Park, Ill), CAT scan of the abdomen and pelvis, bone scan, chest radiograph (followed by a CAT scan of the chest, if any abnormalities were observed), complete blood count, and serum chemistry profile. All patients were evaluated, and all therapy was administered in the Warren G. Magnusson Clinical Center of the NIH, after written informed consent was obtained.

Patients who were eligible for study were men who had histologically confirmed adenocarcinoma of the prostate, distant metastasis confirmed by either bone scan and/or CAT scan (i.e., stage D2 disease), and confirmed disease progression after hormone therapy. All patients had to have failed therapy with combined androgen blockade (medical or surgical castration in combination with a peripheral androgen receptor-blocking agent, such as flutamide). In addition, patients receiving androgen receptor-blocking agents as their last form of therapy had confirmed disease progression after drug withdrawal. Nonsurgically castrated patients continued to receive luteinizing hormone-releasing hormone agonist while on study. Patients had to be off other forms of therapy for at least 4 weeks prior to protocol entry.

All patients had measurable disease by either bone scan, CAT scan, or PSA. Patients whose only evidence of disease progression was PSA must have had prior evidence of metastasis by either bone scan or appropriate radiographic study. Other eligibility criteria included: Eastern Cooperative Oncology Group performance status of 0–2; preserved hematological, hepatic, and renal function; and castrate levels of serum testosterone. Patients with a history of brain metastasis, new lesions in the cortex of weight-bearing bones, or obstructive uropathy or with a QTc interval of >0.5 s on a standard 12-lead ECG were excluded.

Response Criteria. Response to therapy was assessed every 2 months, and toxicity was assessed monthly. A complete response required resolution of all signs of disease for a duration of at least 1 month: normalization of PSA, resolution of all soft tissue lesions, and disappearance of all lesions on bone scan. A PR required a decrease by >50% of the sum of the product of the perpendicular diameters for all soft tissue lesions, a decrease in PSA by >80% for at least 1 month, or a resolution of lesions on bone scan in the absence of new lesions. PD required: a >50% increase in PSA, a >25% increase in the sum of the product of the perpendicular diameters for all soft tissue lesions, or the appearance of new lesions (either soft tissue or on bone scan). For PD to be scored by PSA criteria alone, a confirmatory PSA determination was required and obtained 2 weeks after the value representing a >50% increase. Patients who experienced decline in performance status, 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 one objective parameter while meeting the criteria for PD by another parameter were scored as having PD. Patients who did not experience a response or exhibit PD were scored as having stable disease, if they remained clinically stable for a period of at least 2 months. All responses were independently confirmed by two senior staff observers.

Quality of Life Assessment. Starting with patient 13, patients were asked to complete the Functional Living Index-Cancer questionnaire prior to receiving treatment and at the 2-month time point. The content, administration, and analysis of the Functional Living Index-Cancer were as described previously (26, 27).

Treatment. Treatment consisted of oral tamoxifen 80 mg/m² b.i.d. (160 mg/m²/day) in the form of tamoxifen citrate (Nolvadex; Zeneca Pharmaceuticals Inc., Wilmington, DE). The first six patients entered onto study initially received 100 mg/m² b.i.d. (200 mg/m²/day). Treatment was administered on a continuous basis, reevaluated monthly, and discontinued for toxicity higher than grade 3 (National Cancer Institute Common Toxicity Criteria) or disease progression. In patients experiencing grade 3 toxicity, drug was restarted with a 20% reduction in dose once symptoms had decreased to below grade 1. Patients experiencing grade 4 toxicity were not retreated. In three patients who experienced grade 2 gastrointestinal toxicity (i.e., vomiting), tamoxifen was administered at 40 mg/m² four times a day (160 mg/m²/day).

Because no toxicity criteria exists for prolongation of QTc, patients with a QTc interval of >0.5 s were considered to have grade 3 toxicity. The QTc interval was determined from a standard 12-lead ECG, according to the following equation: QTc = (QT interval/square root of the r–r interval). ECGs were obtained every week for the first 4 weeks and then monthly thereafter.

Pharmacokinetics. Tamoxifen plasma concentrations were determined as described. Briefly, tamoxifen was isolated from plasma by liquid-liquid extraction using methyl tert-butyl ether. Samples were then separated on a Waters Nova-Pak C-18 (3.9 × 150 mm) column (Milford, MA) using a gradient mobile phase containing acetonitrile with 0.1% triethylamine-0.05 M ammonium acetate (pH 7.0) on a Hewlett Packard 1090 Series II Liquid Chromatograph (Palo Alto, CA) equipped with a photodiode-array detector. Plasma samples were obtained pre-treatment and then at each monthly clinic visit for all enrolled patients. Posttreatment plasma samples were used for estimating steady-state tamoxifen concentrations. All blood samples were taken from venous lines and collected into heparinized tubes. Plasma was stored at −70°C until analysis. Posttreatment samples were sorted based upon tamoxifen dose level, and the mean and SD were determined for each dose level.

Statistical Methods. All patients entered onto study were formally registered, and all registered patients were included in the data analysis. Periodically, chart reviews and data entry methods were evaluated by an external panel of individuals to ensure the accuracy of data.

This study was designed as a Phase II trial, with two stages for accrual: if at least one response or stabilization was observed in the first 14 patients, then accrual would continue until at least

RESULTS

Patient Characteristics. Patient characteristics are listed in Table 1. A total of 34 patients were enrolled onto study. Patients had a median performance status of 1 (range, 0–2), Osseous disease was present in 33 patients (97%), 10 patients (29%) had evidence of soft tissue disease, and 32 patients (94%) had an elevated PSA level. Six, 50, and 32% of patients had Gleason scores of 2–4, 5–7, and 8–10, respectively; four biopsies (12%) were from sites other than the prostate gland and were not scored. The median time from diagnosis of prostate cancer to study entry was 41 months (range, 15–184 months).

Prior treatment is listed in Table 2. All patients had received prior treatment with combined androgen blockade. Twenty-one patients (62%) received further hormone therapy (i.e., second- or third-line hormone therapy), after failing primary hormone therapy. Twenty patients (59%) had received chemotherapy, and 13 (38%) had received external beam radiation therapy for metastatic disease. Considering both hormone and chemotherapy, patients had received a median of three prior treatment regimens (range, one to eight prior regimens). In this study, patients received a total of 84 cycles (months) of therapy with tamoxifen (median, 2.3 cycles; range, 0.3–9.0 cycles).

Toxicity. Two patients withdrew from study prior to receiving drug, and one patient withdrew after 2 weeks of therapy, and these three patients did so in the absence of disease progression or toxicity; 31 patients were, therefore, evaluable for toxicity. Toxicities are listed in Table 3. Overall, 11 patients (35%) required dose reduction due to grade 3 toxicity: 8 patients (26%) experienced ataxia only, 1 patient (3%) prolongation of QTc only, and 2 patients (6%) experienced both. The first 6 patients on study received tamoxifen at 100 mg/m² b.i.d. (200 mg/m²/day). Three (50%) of these first six patients experienced grade 3 toxicity. Subsequent patients received tamoxifen at 80 mg/m² b.i.d. (160 mg/m²/day), and of these, 8 patients (29%) experienced grade 3 toxicity (1 patient experienced prolongation of QTc only, 7 patients experienced ataxia only). With only one exception, grade 3 toxicities due to tamoxifen resolved within 4 days of stopping the drug.

Abnormalities of gait appeared to be due to alterations in the function of proprioception related long tracts. Gait alterations were characterized by abnormal heel-to-toe walking, episodic objective clinical findings of decreased proprioception function in the lower extremities, and an absence of clinical measures of cerebellar dysfunction. Gait alterations did not resolve after discontinuation of drug in one patient who experienced grade 3 ataxia. Work-up revealed symptomatic orthostatic hypotension. This patient had concurrent cardiac disease and was on blood pressure-lowering medications (including a long-acting nitrate, a calcium channel blocker, and an angioten-
sin-converting enzyme inhibitor). Reduction in medication dosage led to symptomatic improvement. Three patients (9.7%) experiencing grade 2 vomiting requested and received dose reductions. Of these three patients, one was later found to have tumor causing gastric outlet obstruction. The second patient experienced a syndrome consistent with viral enteritis and, shortly thereafter, resumed therapy at full doses without symptoms. Gastrointestinal symptoms persisted in the third patient, despite two separate dose reductions; endoscopy revealed mild diffuse gastritis.

All other toxicities had an unclear relationship to tamoxifen therapy. Specifically, patients were extensively counseled to report any visual changes; six such minor and transient episodes were reported. There was no clear pattern to the symptomatology, and immediate examination by an ophthalmologist failed to reveal any objective findings. Therapy was continued in all cases, and symptoms did not recur. Likewise, there was no clear pattern to neurosensory changes, which were minor in nature and variously consisted of subjective changes in taste, hearing, and distal light touch.

Pharmacokinetics. Plasma steady-state tamoxifen concentrations as a function of dose are listed in Table 4. Plasma concentrations from all patients who were receiving a given dose of tamoxifen for more than a month were averaged and ranged from 1.71 ± 0.27 (mean ± SD) to 2.94 ± 1.15 μM for patients receiving 90 and 200 mg/m²/day tamoxifen, respectively. There was no association between plasma tamoxifen concentration and toxicity ($P = 0.44$, two-sided $t$ test; Fig. 1). Likewise, there was no significant difference ($P = 0.40$) in the concentration of tamoxifen at the 1-month time point between patients who experienced PR or stable disease (2.80 ± 0.26 μM; mean ± SE) and those who experienced PD (3.20 ± 0.60).

Table 3 Toxicity profile

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
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<tr>
<td>Anorexia</td>
<td></td>
<td>12</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Atrial dysrhythmia</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>Constipation</td>
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<td>3</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diarrhea</td>
<td></td>
<td>2</td>
<td></td>
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<td></td>
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<tr>
<td>Edema</td>
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<td></td>
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<tr>
<td>Fatigue</td>
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<td>9</td>
<td>3</td>
<td></td>
<td></td>
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<tr>
<td>Fever</td>
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<td>2</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gait</td>
<td></td>
<td>6</td>
<td>4</td>
<td>10</td>
<td></td>
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<tr>
<td>Hot flashes</td>
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<td>Hypotension</td>
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<td>Infection</td>
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<td></td>
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<tr>
<td>Lightheadedness</td>
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<td>8</td>
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<td></td>
<td></td>
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<tr>
<td>Memory</td>
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<td>4</td>
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<tr>
<td>Nausea</td>
<td></td>
<td>10</td>
<td>6</td>
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<tr>
<td>Neurosensory toxicity</td>
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<td>Prolonged QTc interval</td>
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<td></td>
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<tr>
<td>Visual disturbance</td>
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<td>6</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td>6</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
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<td></td>
<td></td>
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</tr>
</tbody>
</table>

Table 4 Plasma concentrations of tamoxifen in patients receiving daily p.o. tamoxifen

<table>
<thead>
<tr>
<th>Dose level (mg/m²/day)</th>
<th>No. of patients</th>
<th>Concentration (μM)*</th>
</tr>
</thead>
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<tr>
<td>90</td>
<td>3</td>
<td>1.71 ± 0.27</td>
</tr>
<tr>
<td>120</td>
<td>4</td>
<td>2.08 ± 0.45</td>
</tr>
<tr>
<td>160</td>
<td>18</td>
<td>2.96 ± 1.32</td>
</tr>
<tr>
<td>200</td>
<td>6</td>
<td>2.94 ± 1.15</td>
</tr>
</tbody>
</table>

* Values represent means ± SD.

Fig. 1 Plasma tamoxifen concentrations as a function of duration of therapy for 31 men receiving treatment with high-dose tamoxifen. ●, plasma concentrations drawn from patients from within 10 days prior to experiencing grade 3 toxicity; □, plasma concentrations from all other patients.

Response and Survival. Of 34 patients enrolled, 30 patients were evaluable for response and survival: 2 never received study drug, 1 removed himself from study after 2 weeks, and 1 was removed after 3 weeks due to grade 3 neurotoxicity which preceded study entry. None of these four patients exhibited clinical evidence of disease progression at the time at which they were removed from study.

One patient (3.3%) experienced a PR, based upon a >80% reduction of PSA for 9 months. Six patients (20%) were scored as having stable disease. The overall PR plus stable disease response rate was 23% (95% confidence interval, 10–42%). Twenty-three patients (77%) exhibited disease progression on or prior to initial restaging. With continued follow-up, 29 patients (97%) experienced disease progression. Disease progression was scored on the basis of the following: PSA (22 patients), bone scan (16 patients), soft tissue (3 patients), intractable pain (2 patients), spinal cord compression (2 patients), and hydronephrosis (1 patient). No improvement in soft tissue or osseous disease was observed. Of interest, stabilization of exponentially rising PSA was observed in six individuals, coincident with tamoxifen treatment (Fig. 2).

Median time to disease progression was 2.1 months (range, 0.3–9.0 months; Fig. 3). At the time of analysis (June 1997), the median potential follow-up time was 28.6 months. Median survival was 10.5 months (Fig. 4). Currently, 7 patients (23.3%) are alive.
Quality of Life. Of the 18 patients who were asked to complete questionnaires, 12 (75%) completed questionnaires for both the pretreatment baseline and the 2-month time points. Two patients (17%) experienced an overall improvement in quality of life indices, and two (17%) had stable scores, for a combined stable plus improved rate of 34%, whereas 8 patients (66%) experienced a decline in quality of life indices.

DISCUSSION
Therapy for hormone-refractory prostate cancer is limited. An improved understanding of the underlying biology of prostate cancer provides the basis for targeted therapeutic approaches. One such potential target is TGF-β (19–22). Whereas TGF-β inhibits the growth of normal prostate cells, there appears to be early loss of inhibition during carcinogenesis. Recent studies have shown that high concentrations of tamoxifen (i.e., 1 mM) inhibit PKC in prostate cancer cells, in association with direct activation of the TGF-β signaling pathway (9). This is accompanied by induction of the cell cycle inhibitory protein, p21waf1/cip1, dephosphorylation of retinoblastoma protein (Rb), and cell cycle arrest at the G1-S phase interface. PKC inhibition has also been shown to be an important modulator of TGF-β signaling in cell types other than prostate (30). High plasma concentrations of tamoxifen can be attained with high-dose tamoxifen therapy, where it has been successfully applied to inhibit PKC in the treatment of patients with astrocytoma (23, 24, 31–35). This study was undertaken to determine whether high-dose tamoxifen therapy was associated with clinical activity in patients with metastatic prostate cancer.

Although tamoxifen has previously been tested in clinical studies involving patients with metastatic prostate cancer, this study differs in a number of important ways (36–38). In prior studies, tamoxifen was used as an estrogen agonist/antagonist and, thus, was given at conventional doses. Furthermore, patients were not uniformly hormone-refractory, nor were they uniformly castrate at the time of treatment. Because estrogens, such as diethylstilbestrol, have known activity in prostate cancer through their ability to suppress testicular androgen secretion and because tamoxifen has known estrogenic agonist activity, castrate levels of testosterone are necessary to rule out a hormone-based mechanism (39). In this study, castrate levels of testosterone were documented prior to treatment, and luteinizing hormone-releasing hormone agonists were continued for patients already on such therapy.

Prior studies suggested that patients would be able to tolerate tamoxifen at 100 mg/m² b.i.d. (200 mg/m²/day). Trump et al. (23) reported that high-dose tamoxifen therapy was well tolerated when it was given at 150 mg/m² b.i.d. (300 mg/m²/day) for 13 days of a 28-day treatment cycle, after an initial loading dose. In other studies, tamoxifen was administered to women with breast cancer for up to 1 year and to both men and women with renal cell carcinoma at 100 mg/m² b.i.d. (200 mg/m²/day), and it was well tolerated (40, 41). In this study, three of the first six patients treated at the 100 mg/m² b.i.d. level experienced grade 3 toxicity, and subsequent patients were, therefore, reduced to 80 mg/m² b.i.d. (160 mg/m²/day). Differences in the study population (e.g., older males versus females) may underlie the increased toxicity observed at the 200 mg/m²/day dosing level initially used in this study. Whereas 29% of patients experienced grade 3 toxicity at the 160 mg/m²/day dosing level in this study, symptoms came on gradually, were easily detectable at early onset, and were reversible with discontinuation of drug. Steady-state plasma tamoxifen concentrations in patients receiving 160 mg/m²/day were 2.96 ± 1.32 μM and were, thus, in the range in which in vitro growth inhibition was observed.

Fig. 2 Examples of different serum PSA response profiles in patients receiving high-dose tamoxifen therapy. A, patients whose PSA values stabilized after treatment with tamoxifen. Shown are PSA response profiles from the six patients whose exponentially rising PSA levels stabilized after treatment with tamoxifen. The vertical line (time = 0) indicates when treatment with tamoxifen began. Prior to treatment (left), exponentially increasing PSA values are seen, indicative of the nature of PD at the time of study entry. After treatment (right), PSA values stabilized to within 10% of the on study PSA value for the indicated times. B: for comparison purposes, the PSA profiles of two individuals who experienced PD (●) and PR (□).
Within the concentration ranges attained in this study, plasma tamoxifen concentration did not appear to correlate with either response or toxicity. However, all concentrations except one were $>1 \mu M$ and were, thus, in the range in which direct growth-inhibitory effects were observed \textit{in vitro}. Therefore, once micromolar concentrations are attained, other factors appear to account for differential response and toxicity.

Grade 3 toxicities were limited to those previously associated with high-dose tamoxifen therapy, namely, gait disturbances and prolongation of QTc interval (23). Of note, the schedule of ECG monitoring used in this study to detect prolongation of QTc interval is felt to be optimal and is recommended for all patients on high-dose tamoxifen therapy. All abnormalities were detected within the first month, except in one patient, thus supporting weekly monitoring within the first month. In one patient, prolongation QTc was detected on a routine monthly ECG and appeared to be

Fig. 3 Time to disease progression in patients receiving high-dose tamoxifen therapy for hormone-refractory adenocarcinoma of the prostate. Time to disease progression was determined from the day of study entry. The probability of remaining progression free was calculated according to the method of Kaplan and Meier, as described in "Materials and Methods."

Fig. 4 Survival of patients receiving high-dose tamoxifen therapy for hormone-refractory adenocarcinoma of the prostate. Survival was determined from the day of study entry. The probability of survival was calculated according to the method of Kaplan and Meier, as described in "Materials and Methods."
associated with binge alcohol consumption. Alcohol consumption may have altered metabolism of tamoxifen by the liver (a known site of tamoxifen metabolism) because abstinence was associated with resolution of the conduction defect once drug was restarted (38). Whereas a retinopathy has been associated (rarely) with both conventional and high-dose tamoxifen therapy, no eye toxicity was observed in patients on high-dose tamoxifen in this study (42).

Although not used as a criteria for scoring stable disease, a notable stabilization in the rate of PSA increase was observed coincident with commencing high-dose tamoxifen therapy. Because declines in PSA have been associated with longer survival in other clinical trials, a prospective analysis of the prognostic significance of this form of active PSA stabilization is warranted. The response rate associated with high-dose tamoxifen therapy in this study does not warrant clinical application outside of an investigational setting at this time. However, the identification of clinical activity in a heavily pretreated patient population, with therapy that was shown to directly activate TGF-β signaling pathways in preclinical studies, identifies high-dose tamoxifen therapy as worthy of further clinical investigation. It is possible that high-dose tamoxifen therapy may be more effective in a less heavily pretreated patient population or more appropriately applied as an adjuvant to local therapy.

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