A Randomized Phase II Trial of the Antiangiogenic Agent SU5416 in Hormone-Refractory Prostate Cancer

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ABSTRACT

Purpose: **To assess the activity of the antiangiogenic agent and VEGFR2 inhibitor SU5416 in hormone-refractory prostate cancer.**

Patients and Methods: **Thirty-six chemotherapy naïve patients were randomized to treatment with SU5416 (145 mg/m^2) and dexamethasone premedication or dexamethasone alone. Patients in the control arm could cross over to experimental therapy after progression. Prostate-specific antigen (PSA) was measured every 2 weeks, and radiological evaluation was performed every 8 weeks. *In vitro* assessment of SU5416 on PSA secretion was assessed in the LNCaP cell line. Baseline serum basic fibroblast growth factor and plasma vascular endothelial growth factor (VEGF) were explored as prognostic factors.**

Results: **VEGF receptor-2 expression is detectable in prostate cancer cell lines, and SU5416 inhibited *in vitro* PSA secretion. No effect of SU5416 on PSA secretion or time to progression is detectable in patients. VEGF and basic fibroblast growth factor were not prognostic. Headache and fatigue were the most common SU5416 toxicities, but hyperglycemia, hyponatremia, lymphopenia, infection, and adrenal suppression, all attributable to steroids and the required central line, were common.**

Conclusion: **No disease modifying effects of SU5416 were detectable in this small study. Modest toxicity, an inconvenient administration schedule, and availability of other VEGFR-targeted agents support the decision to halt further evaluation of SU5416 in prostate cancer.**

INTRODUCTION

Although androgen ablation and secondary hormonal maneuvers are effective in treating metastatic prostate cancer, there are limited options for hormone-refractory disease. To date, chemotherapy has been shown to improve quality of life in symptomatic patients but not to improve survival (1, 2). There is thus no standard treatment for the many patients with hormone-refractory disease who present with an asymptomatic rise in their prostate-specific antigen (PSA) or asymptomatic radiological progression. Nonetheless, a PSA rise is a harbinger of clinical metastatic disease, and the median survival from development of asymptomatic hormone-refractory disease to death is only about 20 months (3). In addition, the majority of patients with metastatic prostate cancer are elderly and often have comorbid diseases. As a result, prolongation of time to progression, as opposed to disease eradication, is a reasonable therapeutic goal.

Antiangiogenic agents have been reported to be cytostatic in the preclinical setting and thus potentially capable of prolonging time to disease progression. A variety of different antiangiogenic agents, such as inhibitors of the vascular endothelial growth factor (VEGF) growth factor pathway, are under development. VEGF is secreted by many different solid tumors including prostate cancer (4), and VEGF serum, plasma, or urine levels are correlated with patient outcome in both localized as well as disseminated prostate cancer (5–7). VEGF interacts with a variety of growth factor receptors on endothelial cells. The receptor most important for endothelial cell proliferation is VEGFR2 (kinase domain receptor, fetal liver kinase 1; Ref. 8). VEGFR2 is a classical receptor tyrosine kinase that when activated dimerizes and signals through the mitogen-activated protein kinase kinase pathway (8). Small molecule inhibitors of the VEGFR2 tyrosine kinase have been developed, and one of these, SU5416, is the subject of this investigation.

SU5416 is a competitive inhibitor of VEGFR2 with respect to ATP exhibiting a K_i of 0.16 μM (9). SU5416 inhibits VEGF-stimulated VEGFR2 phosphorylation and endothelial cell proliferation *in vitro* with an IC_{50} of 1.0 μM and 0.04 μM, respectively (10). Solubility problems necessitate that SU5416 be dissolved in a Cremophor plus ethanol vehicle for clinical administration, and this requires coadministration of dexamethasone or other steroids to prevent hypersensitivity reactions (11, 12). Phase I studies showed that the drug was generally tolerable, with headache, nausea, and vomiting being the dose-limiting toxicities (11, 12). Serum elimination half-life is on the order of 1 h (11, 12), but some preclinical studies suggested that intracellular half-life is much longer (13). The recommended Phase II dose and schedule is 145 mg/m^2 twice weekly.

Because the drug is expected to be cytostatic and because dexamethasone can lead to PSA and clinical responses in patients with hormone-refractory prostate cancer (14), we elected to perform a randomized Phase II study in which patients were allocated to receive either steroids alone or SU5416 along with the required steroid premedication. The primary end point was progression defined by standard radiological or PSA criteria (15, 16). Although the use of PSA only as a marker of progression is

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controversial, the strong prognostic value of a PSA rise and the Phase II exploratory nature of the trial makes the use of PSA criteria reasonable. Patients assigned to the steroid alone arm had the opportunity to cross over to the experimental agent at the time of protocol defined progression. Serum and plasma based angiogenic factors [VEGF and basic fibroblast growth factor (bFGF)] were explored as possible predictive, prognostic, or pharmacodynamic markers.

PATIENTS AND METHODS

Patients. Eligible patients were required to have progressive prostate cancer as defined by two or more serial rising PSA values of at least 5 ng/ml obtained at least 2 weeks apart, or progressive radiological disease, following androgen ablation, an antiandrogen, and antiandrogen withdrawal. Additional hormonal manipulations and palliative radiotherapy were allowed, but prior systemic cytotoxic therapy was an exclusion criteria. Patients were required to have normal organ function defined by creatinine < 2.0 mg/ml, WBC $> 3000/\mu l$, platelet count $> 75{,}000/\mu l$, aspartate aminotransferase $< 2.5 \times$ institutional upper limit of normal, and bilirubin < 1.5 mg/dl. Patients with serious coronary artery disease, recent myocardial infarction, severe peripheral vascular disease, or a history of arterial or venous thrombosis in the last 3 months were excluded. Patients could have no medical contraindications to high-dose steroids, and all provided written, signed, informed consent. The clinical protocol was conducted under a contract from the National Cancer Institute to the University of Chicago, and approved by the University of Chicago Cancer Research Center Clinical Trials Review Committee, and by the relevant institutional review boards.

Treatment and Patient Monitoring. Patients were randomized in a 1:1 fashion using sealed envelops to receive either high-dose steroids or high-dose steroids before SU5416 145 mg/m^2 i.v. over 30 min twice a week. The high-dose steroid treatment was dexamethasone, 10 mg orally twice, 12 h apart, followed by 0.5 mg orally on the following day. After 2 weeks of therapy, the 10-mg dexamethasone dose was decreased to 4 mg. Patients receiving SU5416 were also treated with 1 mg of Coumadin daily for thrombosis prophylaxis and received H1 and H2 blockers as premedication. Patients in the steroid alone control group had the opportunity to receive experimental SU5416 at the same dose and schedule at the time of protocol-defined progression.

Patients were monitored with liver function tests, electrolytes, and PSA every other week and physical exam, complete blood count, and corticotropin stimulating test every 4 weeks. Computed tomography and bone scans for radiological disease evaluation were performed at baseline and every 8 weeks. Progressive disease was defined as a single rise in the PSA of 25% over the nadir (as long as the rise was at least 5 ng/ml or back to baseline), a new bone lesion, or evidence of progressive disease by standard Response Evaluation Criteria in Solid Tumors criteria on radiological follow-up (15, 16). These criteria are consistent with the published recommendations except that a second confirmatory PSA rise above 25% was not required. Patients were allowed to stay on treatment beyond protocol-defined progression at the discretion of the investigator and the patient, if therapy was tolerated, and if progression was asymptomatic.

All patients were also monitored for adrenal suppression as a potential toxicity of intermittent steroid administration. A standard adrenocorticorticotropic hormone stimulation test was performed using 0.25 mg of Cosyntropin (i.v.) and measuring baseline as well as 60 min serum cortisol levels after infusion. Patients with a rise in the serum cortisol level of at least 7 $\mu g/ml$ to a value of at least 18 $\mu g/ml$ were classified as having a normal adrenal axis; those with a serum cortisol rise of at least 7 $\mu g/ml$ but to a level of <18 $\mu g/ml$ were classified as having a borderline abnormal adrenal axis, and those with a serum cortisol rise of <7 $\mu g/ml$ were classified as having an abnormal adrenal axis.

***In Vitro* Studies.** *In vitro* studies were conducted simultaneously with the clinical study. Cells used for *in vitro* experiments included established human prostate cancer cell lines DU145, PC3, and LNCaP, HELA for a positive VEGFR2 protein-staining control, and the lung cancer cell line NCI-H23 as a negative VEGFR2-staining control (17). All cell lines were obtained from American Type Culture Collection (Manassas, VA) and propagated in the recommended serum-containing medium. Short-term normal human prostate cancer cells were isolated and propagated as described previously (18).

To assess the effect of SU5416 on *in vitro* PSA secretion, LNCaP cells were seeded at a density of 3×10^4 cells/9.6 cm^2 and were treated with various concentrations of SU5416 (SUGEN, Inc., San Francisco, CA) for 24 h. Supernatant was collected, and PSA concentration, relative to the concentration in untreated controls, was measured using a microparticle enzyme immunoassay (IMX System; Abbott Laboratories, North Chicago, IL). Three individual experiments were conducted in triplicate.

VEGFR2 expression was determined after lysis of exponentially growing cells in RIPA buffer ($1\times$ PBS, 1% IGEPAL CA-630, 0.1% SDS w/v, 0.5% Na-deoxycholate) with inhibitors (10 $\mu l/ml$ phenylmethylsulfonyl fluoride, 15 $\mu l/ml$ $NaVO_4$, and 30 $\mu l/ml$ Aprotinin). Protein lysate (50 μg) was separated on a denaturing 7.5% SDS-polyacrylamide gel and transferred to a nitrocellulose membrane. Equal loading was confirmed by Ponceau S staining, and the protein was detected with a VEGFR2 specific antibody [SC-FLK-1(A3), 1:500 dilution; Santa Cruz Biotechnology, Santa Cruz, CA], a secondary antibody linked to horse radish peroxidase and detected using enhanced chemiluminescence (Supersignal ECL; Pierce Biotechnology, Rockford, IL).

Ancillary Markers. All patients consenting to the treatment protocol were required to participate in a protocol assessing various angiogenesis biomarkers in concurrently performed treatment protocols using SU5416. Serum and EDTA-plasma were collected before therapy and after 8 weeks of therapy and stored at $-70°C$ until batch analysis. Data that became available after protocol design suggested that SU5416 had minimal independent effects on circulating VEGF (19), and this was supported by our limited evaluation of 23 patients with colon cancer, mesothelioma, melanoma, and prostate cancer treated on Phase II trials with SU5416 (20). Therefore, final analysis focused on the prognostic and predictive value of pretherapy plasma VEGF. Because another major factor for tumor angio-

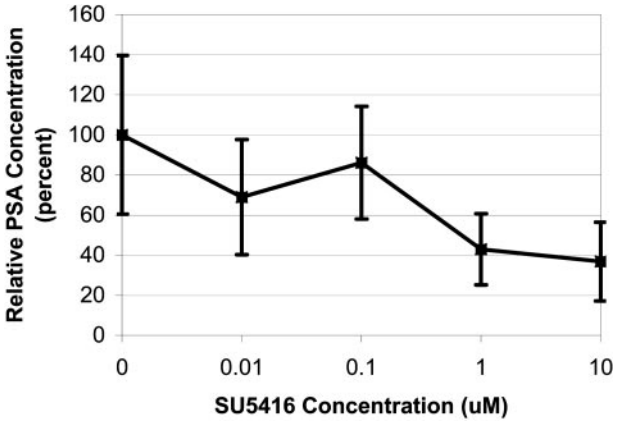

Fig. 1 Effect of SU5416 on prostate-specific antigen (PSA) *in vitro* secretion by LNCaP. PSA in the media was assessed from triplicate wells of exponentially growing LNCaP cells treated with the indicated concentrations of SU5416 for 24 h. SDs for a combined three independent experiments are noted. Fitting an ANOVA model to PSA concentration and log(SU5416) concentration reveals a significant dose effect at the $P = 0.0083$ level. Data were analyzed on absolute PSA scale, although concentrations are shown relative to the baseline mean.

genesis is bFGF, and this factor has been reported to be elevated in the serum of patients with prostate cancer (21), pretherapy serum bFGF was also examined as a possible prognostic or predictive factor.

VEGF and bFGF were measured by Quantikine ELISA kits according to the manufacturers instructions (R&D Systems, Minneapolis, MN).

Statistics. Because the expected effect of an antiangiogenic agent is to prevent or slow disease progression, the primary end point of the trial was time to progression in the two randomized groups. Since further evaluation of this agent, which required twice weekly i.v. administration and high doses of steroids, would only be justified if a major effect on time to progression were observed, a target improvement in the hazard ratio of 2 was chosen. Because this was an exploratory, Phase II trial, generous α and β errors of 0.1 and 0.2 were chosen. Assuming an exponentially distributed time to progression with a 3-month median value in the control group, a two-sided log-rank test thus required 30 patients/group to detect a significant difference in time to progression with 80% power.

In February 2002, SUGEN announced that further development of SU5416 would be halted because of lack of appreciable responses in Phase II trials and failure of the agent to prolong survival in a Phase III trial of 5-fluorouracil/leucovorin with or without SU5416 in metastatic colon cancer. An interim analysis of data on this trial as of July 3, 2002 suggested that it would be highly unlikely that the primary objective would be met, and the study was closed to further accrual with a total of 36 patients. With this study size, the power to detect a hazard ratio of 2 with the specified type I error rate is only 60%, and only a hazard ratio of 2.7 could be detected with the protocol-specified 80% power.

In addition to the primary end point of time to progression, average relative PSA velocities in the two groups of patients were compared (22). The effects of plasma VEGF and serum bFGF on the time to progression hazard function were examined, using a standard Cox proportional hazards regression model (23). Because of preclinical observations suggesting an effect of SU5416 on PSA secretion (see below), an alternative time to progression analysis in which the PSA value 2 weeks after initiating therapy was used as the "baseline" was explored. Toxicity data were evaluated by determining the number of adverse events per treatment cycle and fitting a generalized estimating equation model using a logit link function (24). *In vitro* data on PSA secretion were analyzed by randomized blocks ANOVA (blocking on experiment number).

RESULTS

SU5416 Effect on PSA Secretion *in Vitro*. LNCaP cells were treated with various doses of SU5416 *in vitro*. As previously reported for other tumor cell lines (10), there was no effect on cell growth up to concentrations of 100 μM (data not shown). Nevertheless, there was a significant effect of SU5416 on PSA secretion with an approximate 50% decrease with a 1 μM SU5416 concentration (Fig. 1). To explore this further, various prostate cancer cell lines and normal human prostate epithelial cells in culture were evaluated for the presence of VEGFR2, the putative target of the drug. Fig. 2 shows that VEGFR2 is highly expressed in two of three cancer cell lines, including the LNCaP cell line used for the PSA secretion studies, but not in normal prostate epithelial cells.

SU5416 Effect on Time to Progression and PSA Kinetics in Patients. Patients were enrolled from seven different institutions within the University of Chicago Phase II Network between July 2000 and April 2002. As noted above, the study

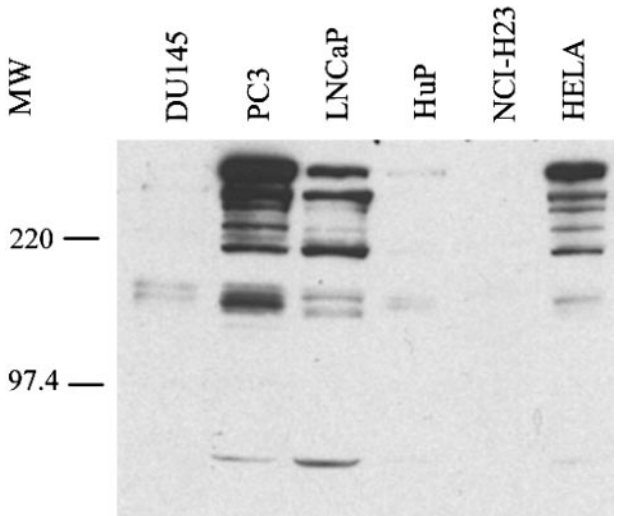

Fig. 2 Expression of VEGF receptor-2 [VEGFR2 (kinase domain receptor)] in prostate cancer cell lines. DU145, PC3, and LNCap are established prostate cancer cell lines; HuP are normal human prostate cells in short term culture (18); NCI-H23 is a lung cancer cell line reported previously to not express VEGFR-2; and HELA cells are a positive control. Unmodified VEGFR-2 has a molecular mass off 150 kDa. The higher molecular weight bands represent glycosylated forms of the receptor (28). *VEGF*, vascular endothelial growth factor; *MW*, molecular weight.

was halted before completing full-planned accrual of 60 patients, and only 36 patients were entered. One patient assigned to the steroid only arm was diagnosed with a second malignancy (metastatic Merkel cell tumor) two weeks after beginning therapy, and one patient enrolled on the SU5416 arm withdrew consent before receiving any therapy. Both patients were considered ineligible for analysis, leaving 18 patients assigned to the steroid alone arm and 16 assigned to the SU5416 arm. Table 1 provides baseline characteristics of the 34 eligible patients. Although patients were fairly typical of an early hormone-refractory population, only 1 patient had PSA only disease, 6 had evidence of visceral disease on computed tomography scan, and the median baseline PSA was 28.8 ng/ml (range, 2.8–878 ng/ml).

The primary end point for the clinical study was time to progression in the two arms. No radiological responses were observed, and PSA response was observed in only 3 patients, 2 in the SU5416 arm and 1 in the steroid alone arm. One patient on the steroid alone arm experienced a PSA response after crossover to the investigational therapy. Progression was defined by radiological end point in only 2 patients, both on the steroid alone arm. PSA rise defined progression in all other patients. The median time to progression was 4 and 10 weeks in the control and experimental arm, respectively, with a P for the difference of 0.35 (log-rank test; Fig. 3).

The *in vitro* effects of SU5416 on LNCaP PSA secretion without effecting cell growth raised concern that PSA is not a reliable marker of tumor burden in this study. If suppression of PSA by SU5416 also occurs *in vivo*, it is reasonable to hypothesize that the PSA 2 weeks after beginning therapy, when little effect of drug on tumor growth is expected, would be lower than baseline values. However, the PSA 2 weeks after beginning SU5416 was marginally higher than the baseline by a mean value of 11.5 ng/ml (paired t test, $P = 0.08$). To further control for an effect of SU5416 on PSA secretion, a separate "landmark" posthoc analysis of time to PSA progression using PSA data from treatment week 2 as the baseline was conducted, but no significant difference between the arms was detectable (log-rank test, $P = 0.10$). Similarly, all patients initially assigned to the steroid arm went on to the crossover portion of the study, and there was no difference in time to progression before *versus* after crossover (log-rank test, $P = 0.22$). Finally, no difference in the average relative PSA velocity (22) was detectable between the two assigned treatment arms (Wilcoxon rank-sum test, $P = 0.86$).

VEGF and bFGF as Prognostic Factors For Progression. Baseline plasma VEGF and serum bFGF values were available in 22 and 21 patients, respectively. Median and range are listed in Table 1. Only five patients had VEGF levels greater than the upper limit of normal listed by the ELISA kit manufacturer, but 19 patients had detectable bFGF (level in normal serum is undetectable). There was no effect on time to progression as a function of baseline VEGF ($P = 0.99$) or bFGF ($P = 0.99$) in a univariate Cox proportional hazards analysis and no interaction between these factors and treatment arm in a multivariate model.

Toxicity. Tables 2 and 3 delineate the most common toxicities by treatment arm and the most serious toxicities, respectively. There was one on-study death in a patient who developed a catheter-related infection. The majority of the toxicities were attributable to steroids as reflected by the lack of significant difference between the event rates (number of events/cycle) observed in the investigational *versus* the control treatment arms. Toxicities directly attributable to SU5416 include headache and fatigue. The increased number of anemia and anxiety/insomnia events in the control group is attributable to only two patients, and thus there is no statistically significant difference in event rates. Thirty patients underwent the required adrenocorticorticotropic hormone stimulation test to assess for adrenal insufficiency sometime during their therapy. Seventeen had a normal adrenal axis, 10 developed a borderline abnormal axis, and 3 had an abnormal adrenocorticorticotropic hormone stimulation test.

DISCUSSION

In this randomized Phase II study of dexamethasone *versus* dexamethasone plus SU5416, we were unable to detect a significant effect of the investigational antiangiogenic agent on prostate cancer growth or on *in vivo* PSA kinetics. However, the small study size dictated that the smallest hazard ratio in time to progression detectable with 80% power is 2.7, and the study specified hazard ration of 2 could only be detected with 60% power. Thus, a clinically significant effect could have easily been overlooked.

We also hypothesized that pretherapy bFGF or VEGF levels might predict whether the tumor of a particular patient is more dependent on the VEGF or bFGF angiogenic pathway. Plasma VEGF levels are prognostic for survival in hormone-refractory prostate cancer (7), and we predicted that if SU5416 is an effective therapy then the prognostic significance of VEGF might be lost in the experimental arm. Neither VEGF nor bFGF baseline levels were prognostic for time to progression, and no interaction between their levels and treatment arm could be

Table 1 Baseline characteristics (N = 34)

Characteristic	Value (range)
Median age	70 (47–84)
Race	
White:	26
Black:	7
Hispanic:	1
Performance Status	
0:	19
1:	15
Disease Location	
Bone:	26
Lymph node:	10
Visceral:	6
PSA[a] only:	1
Original Gleason score	7 (4–9)
Prior therapy	
Androgen ablation	34
Prostatectomy	18
Radiotherapy–prostate	9
Radiotherapy–bone	4
Median Hgb (mg/dl)	12.8 (8.1–16)
Median alkaline phosphatase (unit/liter)	116 (55–776); [nl = 30–120]
Median PSA (ng/ml)	28.8 (2.8–878)
Median VEGF (pg/ml)	58.5 (0–423); [nl = 0–115]
Median bFGF (pg/ml)	7.5 (0–25); [nl = 0]

[a] PSA, prostate specific antigen; VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor.

detected in a Cox proportional hazards model. Therefore, this analysis did not support the possibility that SU5416 had a significant effect on a patient subpopulation. Once again, this may be because of the small size of the study.

Because the principal event defining time to progression was a rise in the PSA, it is possible that SU5416 had a significant effect on disease natural history, but that this was obscured by its effects on PSA secretion. Under the assumption that any effects of SU5416 on PSA secretion are immediate and not cumulative, a landmark analysis of time to progression using the week 2 PSA as baseline, should control for any such acute effects of SU5416 on PSA secretion. This analysis, however, failed to show any difference between the 2 treatment arms. In addition, the preclinical studies suggested that SU5416 could decrease PSA secretion, which would serve to make it appear clinically more useful. The effect of SU5416 on PSA secretion was observed in the LNCaP cell line at a concentration similar to that required for VEGFR2 inhibition in cultured human endothelial cells (10). In addition, LNCaP cells express the VEGFR2 receptor suggesting that the effects on PSA are directly related to the drug's mechanism of action. Although others have observed expression of VEGFR2 in human prostate cancer (25, 26), the PSA actually rose in patients after treatment with SU5416. Although these observations do not prove that SU5416 had no effect on PSA secretion *in vivo*, they do raise the question as to whether the *in vitro* observations have clinical relevance.

The toxicity profile of the drug was not insignificant. Toxicities directly attributable to SU5416 were headache and fatigue. Although these were for the most part manageable, toxicities associated with the required steroid premedication and the central venous access line were troublesome and often serious. They included hyperglycemia, hyponatremia, lymphopenia, and infection. One of the observed infections was central line related and fatal. An increased rate of infection in the investigational arm was also observed in a Phase III study of 5-fluorouracil/leukovorin with or without SU5416 in metastatic colon cancer.[1] In addition, in the colon cancer study, an increase in thrombotic events was observed

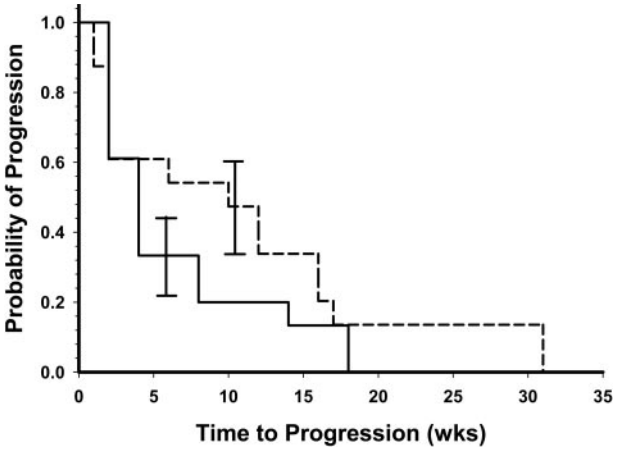

Fig. 3 Time to progression in the two randomized groups. Kaplan-Meier plot for patients randomized to steroids alone are depicted in the *solid* and those randomized to SU5416 plus steroids in the *dashed lines*. *Error bars* represent the SE at the median. The difference between the two curves is not significant (log-rank test, $P = 0.35$).

Table 2 Most common toxicities

Number of events for toxicities where at least five events were recorded during randomized portion of treatment. All events, regardless of grade or attribution are noted. Events occurring after cross-over are not included. Significance of difference in event rate (number of events per cycle) between patients on the dexamethasone alone *versus* the SU5416 arms, as assessed by GEE[a] analysis using a logit link function (see "Materials and Methods"), is indicated

	Dexamethasone alone (43 cycles)	SU5416 + dexamethasone (63 cycles)	*P*
Hyperglycemia	20	34	0.10
Fatigue	6	18	0.03
Anemia	15	7	0.36
Headache	0	17	<0.01
Anxiety/Insomnia	11	2	0.35
Hyponatremia	6	5	0.92
Alkaline phosphatase	6	4	0.70
Anorexia	2	7	0.29
Elevated BUN	3	5	0.69
AST	2	3	0.72
ALT	4	4	0.93
Lymphopenia	2	6	0.14
Diarrhea	1	5	0.19
Dyspnea	1	4	0.19
Flushing	0	5	0.27
Infection	3	2	0.74
Fever	1	4	0.69

[a] GEE, generalized estimating equations; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 3 Serious toxicities

All grade 3, 4, and 5 toxic events, regardless of attribution or treatment arm are listed. This represents the number of events observed in a total of 153 cycles of therapy

Toxicity	Grade 3	Grade 4, 5
Hyperglycemia	23	4
Alkaline phosphatase	6	
Hyponatremia	4	1
Infection without neutropenia	4	1[a]
Lymphopenia	4	
Cardiovascular[b]	4	1
Diarrhea	2	
Fatigue	2	
Headache	2	
Abdominal pain or cramping	1	
Hypertension	1	
Pneumonitis/pulmonary infiltrates	1	
ALT[c]	1	
Constipation	1	
Nausea	1	

[a] Death related to a central line infection

[b] Grade 3 CVA, SVT, pericardial effusion, and DVT (1 each); grade 4 PE.

[c] ALT, alanine aminotransferase; CVA, cerebrovascular accident; SVT, sinus vein thrombosis; DVT, deep vein thrombosis; PE, pulmonary embolism.

[1] S. Percy Ivy, Senior Investigator, Cancer Therapy Evaluation Program, information letter, February 26, 2002.

in the experimental arm, an observation noted in a Phase I trial of gemcitabine, cisplatin, and SU5416 as well (27). Although it was not possible to demonstrate a higher incidence of such events in the experimental arm of the current trial, there is certainly concern that the observed serious cardiovascular events may have been related to either SU5416 or the required central line.

In sum, neither the clinical nor the laboratory data suggested that SU5416 had any disease modifying effect in patients with hormone-refractory prostate cancer. It is critical to note, however, that the study population had mostly macroscopic, radiological detectable disease, and the sample size was small. Thus, a clinically significant effect could have easily been missed, and SU5416 effects in a minimal disease setting were not tested. Nonetheless, no significant activity of this agent has been observed in other Phase II studies nor in a Phase III study of 5-fluorouracil plus leucovorin with or without SU5416 in patients with metastatic colon cancer.[1] Furthermore, more prolonged therapy would likely be necessary to detect a possible disease-modifying effect in a minimal disease setting. The toxicities observed here suggest that such a study would not be prudent. Therefore, additional study of SU5416 in prostate cancer patients is not recommended. Pursuit of other VEGF pathway-targeted agents is however scientifically justifiable and should be pursued.

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