Serum Prostate-Specific Antigen Decline as a Marker of Clinical Outcome in Hormone-Refractory Prostate Cancer Patients: Association With Progression-Free Survival, Pain End Points, and Survival

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Purpose: **Validated end points are lacking for clinical trials in hormone-refractory prostate cancer (HRPC). Controversy remains regarding the utility of a posttreatment decline of prostate-specific antigen (PSA). The purpose of this study was to determine whether posttreatment declines in PSA were associated with clinical measures of improvement in a randomized phase III trial of suramin plus hydrocortisone versus placebo plus hydrocortisone.**

Patients and Methods: **A total of 460 HRPC patients were randomized to receive suramin plus hydrocortisone (n = 229) or placebo plus hydrocortisone (n = 231). All patients had symptomatic, metastatic HRPC requiring opioid analgesics. Clinical end points evaluated included overall survival, objective progression-free survival (OPFS), and time to pain progression (TTPP). An evaluation of overall survival, OPFS, and TTPP as a function of a PSA decline of ≥ 50%, lasting at least 28 days, was undertaken by using a landmark analysis at 6, 9, and 12 weeks. A multivariate analysis of the impact of PSA decline was performed on these clinical end points.**

Results: **A decline in PSA of ≥ 50% lasting ≥ 28 days was significantly associated with a prolonged median overall survival, OPFS, and TTPP, both in the entire group and the suramin plus hydrocortisone group at all three landmarks in both univariate and multivariate analysis.**

Conclusion: **In this prospective, randomized trial of suramin plus hydrocortisone versus placebo plus hydrocortisone, a posttherapy decline in PSA of ≥ 50%, lasting 28 days, was associated with prolonged median overall survival, improved median progression-free survival, and median TTPP. This analysis suggests that a posttreatment decline in PSA may be a reasonable intermediate end point in HRPC trials and calls into question the clinical utility of preclinical assays evaluating the in vitro effect of given agents on PSA secretion.**

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THE LACK OF validated end points for clinical trials in hormone-refractory prostate cancer (HRPC) has long challenged clinical investigators.[1] Although improvement in survival remains the gold standard to demonstrate clinical benefit, this end point is not assessable in phase II studies and may be difficult to evaluate in phase III clinical trials, which are frequently confounded by cross-over designs used to ensure that all patients have access to potentially beneficial therapy. The lack of bidimensionally measurable disease in more than 70% of HRPC patients also precludes using objective responses in measurable disease as an end point. Posttherapy decline of prostate-specific antigen (PSA) has been evaluated in multiple reports and has been recommended as a potential marker of response.[2-4] However, the use of a decline in PSA as an intermediate marker of response has not been prospectively validated, and controversy remains as to its utility.[5,6]

The use of PSA as an intermediate marker of response is further complicated by the fact that PSA levels can be affected by a variety of factors. Corticosteroids have the capacity to cause reductions in PSA and have been shown to possess palliative and antitumor properties.[7] In addition, antiandrogen withdrawal clearly results in PSA declines in approximately 20% of patients.[8,9] Thus, some of the PSA changes noted in older reports in the literature may be attributed to antiandrogen withdrawal or the effect of concurrently administered corticosteroids.

The report that in some preclinical models, some agents result in a PSA decline that is attributed to inhibition of PSA secretion without concurrent cytotoxicity has further confounded the interpretation of posttreatment changes in PSA levels. For example, the discordance between PSA suppression and antitumor activity has been reported with suramin in preclinical in vitro and in vivo models.[10] However, these laboratory observations, reported in a single publication, are of unknown clinical significance. The results of a large, placebo-controlled multicenter randomized trial comparing suramin plus hydrocortisone to placebo plus hydrocortisone have been recently reported.[11] The purpose of this analysis was to determine whether posttreatment declines in PSA were associated with clinical measures of improvement,

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including survival, time to progression, and duration of pain control for patients treated on this trial, the largest prospective phase III trial to date of systemic therapy for HRPC.

PATIENTS AND METHODS

Eligibility Criteria and Treatment Plan

Eligible patients had histologically confirmed adenocarcinoma of the prostate, with painful bone metastases requiring a stable chronic regimen of opioid analgesics. The details of study design, eligibility criteria, and treatment regimen have been reported previously.[11] In brief, eligible patients were stratified by PSA level (≤ 100 ng/mL, > 100 ng/mL) and presence or absence of soft-tissue metastases and were randomized in a double-blind fashion to receive suramin plus hydrocortisone or placebo plus hydrocortisone. The therapy received by each patient was identified (unblinded) only in the event of progressive disease or dose-limiting toxicity (DLT). Progressing patients found to be receiving suramin were withdrawn from the study and observed for survival. Patients receiving placebo were eligible to enter cross-over and receive open-label suramin on the same 78-day regimen. PSA levels were measured weekly during treatment, then monthly after treatment ended. Measurable lesions were assessed at baseline, at week 13, and then every 3 months. Opioid analgesic dosage was continuously adjusted as clinically indicated. Toxicity was graded according to the Cancer and Leukemia Group B expanded common toxicity criteria. If grade 3 or 4 toxicity occurred, dosing was interrupted until the toxicity resolved to grade 2 or baseline. Patients who experienced any persistent (8 weeks or more) or recurrent grade 3 or 4 toxicity without significant antitumor response were considered to have reached DLT, and treatment was discontinued permanently.

Response Criteria

Pain and opioid analgesic use were the primary indicators of response. Each night, patients scored their worst pain over the prior 24 hours (the daily worst pain) from 0 (no pain) to 10 (pain as bad as you can imagine) as part of the Brief Pain Inventory. Each night, patients also recorded their daily opioid analgesic use, which was subsequently converted to morphine equivalents. Pain response was prospectively defined before unblinding of the data and was achieved when, for a minimum of 3 consecutive weeks, pain decreased ≥ three points from baseline while opioid analgesic use either decreased or remained stable (< 15% increase), opioid analgesic use decreased ≥ 33% from baseline while pain either decreased or remained stable (< 2 point increase), or both of these. For patients with baseline pain scores ≥ 2 but less than 3, a reduction to 0 was required to achieve response. Similarly, for patients with baseline daily opioid analgesic use ≥ 5 mg but less than 15 mg (morphine equivalents), a decrease by 5 mg was required to achieve pain response.

Prior reports[2-4] have suggested that posttherapy declines in PSA of ≥ 50% correlate with improved survival. For this reason, patients were retrospectively categorized into one of two categories on the basis of whether a greater than 50% decline from baseline that lasted ≥ 28 days was achieved (for purposes of this report, termed a PSA decline). Performance status was measured weekly with the Validated Revised Rand Functional Limitations Scale (RRFLS), which captured each patient's self-assessment of everyday activities such as self-care and mobility, ranging from a score of 8 (least functional impairment) to 40 (most functional impairment), as well as by physician-determined Karnofsky Performance Status (KPS).

Disease Progression

Objective disease progression was defined as an increase in size of measurable lesions, development of new osseous lesions, new urinary outflow obstruction secondary to tumor that required intervention, new malignant pleural effusion, or new spinal cord compression. In all patients, regardless of their pain response status, demonstration of objective disease progression was considered evidence of treatment failure and resulted in unblinding of treatment. Pain (subjective) progression was prospectively defined as a two-point increase in weekly average of the daily worst pain score or a greater than 15% increase in weekly average of the total daily opioid analgesic intake, each with deterioration from baseline in RRFLS performance status by ≥ eight points. An accompanying decline in RRFLS score was mandated to make disease progression defined by pain, opioid requirements, or both more rigorous and therefore more likely to be clinically significant. Treatment assignment was unblinded when either disease progression or DLT occurred, and patients found to be on placebo were offered open-label suramin. A minimum of 6 weeks on study was required before treatment could be unblinded. Unblinding for disease progression before the 6-week mark required study chair approval.

Statistical Considerations

The objective progression-free survival (OPFS) time, time to pain progression (TTPP), and overall survival time were measured from the first day of treatment with the Kaplan-Meier method.[12] All analyses were performed on an intent-to-treat basis. Thus, patients who progressed on placebo plus hydrocortisone and who were crossed over to suramin plus hydrocortisone were included in the analysis.

To evaluate the association between PSA decline and other measures of outcome, the Kaplan-Meier method was used to compare, overall and within each treatment group, the trends for three end points (OPFS, TTPP, and overall survival) for patients with and without a PSA decline of ≥ 50%. All analyses were performed with the Landmark Method.[13] Three different landmarks were used: week 6, week 9, and week 12. Patients whose survival was shorter than the landmark point were excluded from analysis. This method has been used as a means of reducing the inherent bias of assessing survival as a function of response.

The effect of other variables on the end points was evaluated by fitting a Cox model with that variable.[14] The variables considered were two pretreatment stratification variables (PSA level ≤ 100 ng/mL v > 100 ng/mL and presence or absence of measurable disease) and size of treating center. (Study centers were assigned to one of three categories on the basis of accrual, with the goal of accounting for differing levels of familiarity and expertise with suramin administration that would naturally evolve with increasing enrollment. These arbitrary categories were [a] up to eight patients enrolled, [b] 9 to 23 patients enrolled, and [c] 24 or more patients enrolled.) In addition, age, race, baseline pain medication requirement, RRFLS performance status, KPS, alkaline phosphatase, hemoglobin, and lactate dehydrogenase values were considered. For each end point, the variable was first entered linearly and then (where applicable), entered as a group of tertiles. Models were fitted using the variable alone and the variable in the presence of the treatment group. Any variable with a P value of less than .10 was considered a possible confounder for the end point. Where the linear and the tertile were both significant, the linear form in the multivariate model was used. Once a list of candidate confounders was established, a Cox model was fitted with these confounders and PSA response.[14]

For the combined population (suramin plus hydrocortisone and placebo plus hydrocortisone), models were also fitted with and without a term for treatment group.

RESULTS

From February 1994 to December 1996, 460 patients entered the study: 229 in the suramin plus hydrocortisone group and 231 in the placebo plus hydrocortisone group. All patients enrolled were included in an intent-to-treat analysis, with the exception of two patients (one on each arm) who were randomized but were found to be ineligible and did not receive treatment. The two groups of patients were balanced with regard to age, race, baseline pain score, baseline daily opioid analgesic requirements, RRFLS performance status, KPS, site of disease (bone only *v* bone plus soft tissue), PSA level, hemoglobin level, and prior hormonal therapy, as previously described. Of 230 patients randomized to placebo plus hydrocortisone, 164 (71.3%) crossed over to receive suramin after progressing.

Of 269 suramin patients, the percentage of patients with a ≥ 50% decrease in PSA lasting at least 28 days, was 23%, 39%, and 45% with a 6-week, 9-week, and 12-week landmark, respectively. The respective percentage of 231 patients receiving placebo with a greater than 50% PSA decline was 5%, 21%, and 30%. For all 460 patients enrolled, the percentage with a PSA decline at the three landmarks was 14%, 31%, and 38%. Duration of pain response, time to progression, and overall survival in the two treatment groups have been reported elsewhere.[11] Disease progression occurred in 376 (82%) of the 458 patients and was documented on the basis of objective evidence in approximately 85% of disease progressors. Subjective evidence of disease progression (an increase in pain, analgesic use, or both, combined with deterioration in RRFLS performance status) accounted for 12% and 17% of patients with progressive disease in the suramin and placebo groups, respectively. The details of patterns of disease progression have been reported elsewhere.[11]

Association of PSA Decline With Overall Survival

When the entire cohort (suramin and placebo patients) is considered, a durable decline in PSA was found to be associated with improved median survival at the 6-week landmark (563 *v* 325 days, $P = .0019$), 9-week landmark (596 *v* 344 days, $P = .0009$), and 12-week landmark (597 *v* 374 days, $P = .003$). A decline in PSA in patients randomized to receive suramin was also associated with an increased median survival at the 6-week landmark (532 *v* 312 days, $P = .0033$), 9-week landmark (532 *v* 333 days, $P = .0028$), and 12-week landmark (596 *v* 392 days, $P = .003$). In the placebo plus hydrocortisone–treated patients, there was a trend toward increased survival in patients exhibiting a decline in PSA (600 *v* 337 days at the 6-week landmark, 612 *v* 355 days at the 9-week landmark, and 601 *v* 368 days at the 12-week landmark). However, these trends did not reach statistical significance, perhaps because of the small number of patients with a PSA decline in the placebo-treated patients (Table 1).

Table 1. Association Between PSA Decline (≥ 50% decrease in PSA lasting at least 28 days) at Landmarks and Overall Survival Showing the *P* Value From Log-Rank Test (univariate analysis)

Population Landmark	PSA Decline	N	%	Median (days)	*P* (log-rank)
Combined					
6 weeks	All	346			.0019
	Decline	50	14	563	
	No decline	296	86	325	
9 weeks	All	278			.0009
	Decline	85	31	596	
	No decline	193	69	344	
12 weeks	All	209			.0031
	Decline	80	38	597	
	No decline	129	62	374	
Suramin					
6 weeks	All	175			.0033
	Decline	41	23	532	
	No decline	134	77	312	
9 weeks	All	153			.0009
	Decline	59	39	532	
	No decline	94	61	333	
12 weeks	All	118			.0030
	Decline	53	38	596	
	No decline	65	62	392	
Placebo					
6 weeks	All	171			.1378
	Decline	9	05	600	
	No decline	162	95	337	
9 weeks	All	125			.0578
	Decline	26	21	612	
	No decline	99	79	355	
12 weeks	All	91			.2623
	Decline	27	30	601	
	No decline	64	70	368	

Table 2 shows the *P* values used to screen the variables (potential confounders) for use in the multivariate analysis. Only two variables were excluded from the multivariate analysis on the basis of their performance in this screen: baseline pain medication and race.

A multivariate fit of the effect of PSA decline on overall survival, adjusted for three stratification variables (center size, baseline PSA, and measurable disease) and the screened confounders, did not substantially alter the observation that a PSA response at any of the landmarks resulted

Table 2. *P* Values of Possible Confounders and Their Effect on Overall Survival From Day 0

Predictor	*P*	
	Linear	Tertiles
Measurable disease	< .0001	
Baseline PSA	.0181	< .0001
Size of center*	.0676	.1621
Age†	.1752	.0157
Alkaline phosphatase	< .0001	< .0001
Baseline KPS	< .0001	< .0001
Hemoglobin	< .0001	< .0001
Lactate dehydrogenase	< .0001	< .0001
RRFL total score	< .0001	< .0001
Baseline pain medication†	.6196	
Race†	.9235	

*Defined as small (accrual of one to eight patients), medium (accrual of nine to 23 patients), or large (accrual of 24 or more patients).
†Tertile form used in multivariate analysis.
‡Not included as variables in multivariate analysis.

in an improvement in median overall survival, both in the entire group as well as the suramin group (Table 3). For illustrative purposes, overall survival of the entire cohort of patients as a function of PSA decline at the 9-week landmark is shown in Fig 1.

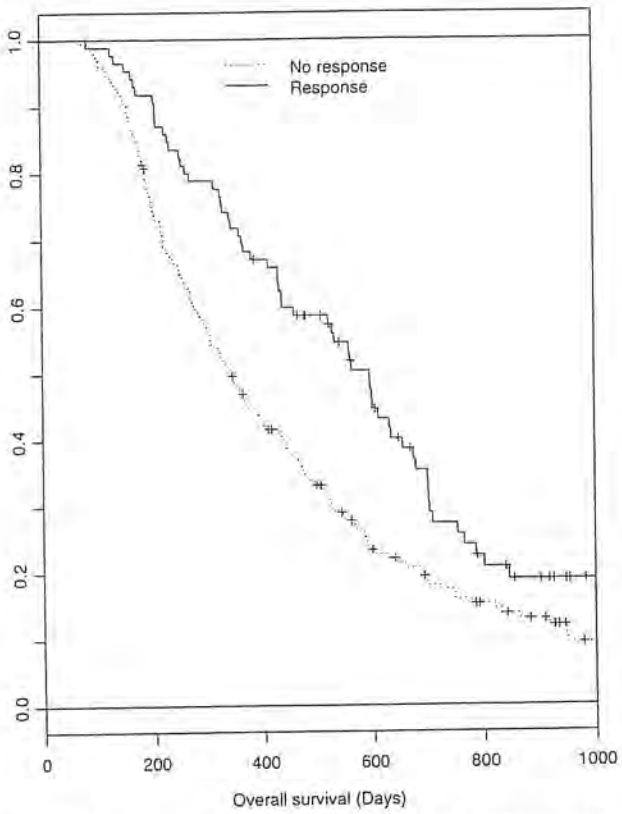

Fig 1. Overall survival (days) by PSA decline at the 9-week landmark (all patients). Median (days): response = 596 days; no response = 344 days (*P* = .0009).

Association of PSA Decline With OPFS

A decline in PSA was also found to be associated with improved median OPFS in the entire group at all three landmarks (170 *v* 88 days at the 6-week landmark, $P = .0027$; 183 *v* 96 days at the 9-week landmark, $P < .00001$; and 193 *v* 122 days at the 12-week landmark, $P < .0001$). In the suramin plus hydrocortisone group and placebo plus hydrocortisone group, a decline in PSA was associated with the OPFS when the 9- and 12-week landmarks were used but did not reach statistical significance when the 6-week landmark was used ($P = .0662$ for the suramin plus hydrocortisone group; $P = .0582$ for the placebo plus hydrocortisone group) (Table 4).

As with the analysis of variables (possible confounders) of the relationship between PSA decline and overall survival, only two variables (baseline pain medication and race) were excluded from the multivariate analysis of the

Table 3. Multivariate Analysis of the Association Between PSA Decline at Landmarks and Overall Survival, OPFS, and TTPP With the Cox Model

Population	Landmark (weeks)	Overall Survival			OPFS			TTPP		
		HR	95% CI	*P* (Cox)	HR	95% CI	*P* (Cox)	HR	95% CI	*P*
Combined	6	1.63	1.14-2.34	.0075	1.70	1.18-2.46	.0045	2.41	1.33-4.35	.0037
	9	1.61	1.18-2.18	< .0024	1.96	1.42-2.72	< .0001	2.00	1.20-3.33	.0075
	12	1.59	1.14-2.23	< .0068	2.19	1.52-3.17	< .0001	1.72	1.00-2.97	.0515
Suramin	6	1.90	1.24-2.91	.0031	1.45	0.92-2.27	.1088	2.46	1.15-5.26	.0197
	9	1.99	1.33-2.99	.0009	1.62	1.05-2.52	.0309	2.58	1.22-5.48	.0135
	12	2.37	1.50-3.75	.0002	2.36	1.41-3.93	.0010	2.49	1.07-5.80	.0350
Placebo	6	1.57	0.68-3.64	.2883	1.97	0.87-4.47	.1065	1.50	0.50-4.46	.4679
	9	1.69	0.99-2.87	.0541	2.41	1.40-4.16	.0016	1.49	0.71-3.13	.2867
	12	1.36	0.77-2.41	.2850	2.17	1.17-4.03	.0142	1.04	0.47-2.30	.9225

NOTE. Table shows the hazards ratio with 95% confidence interval and *P* value (adjusted for potential confounders, including the three stratification variables).
Abbreviations: HR, hazards ratio; CI, confidence interval.

Table 4. Association Between PSA Decline at Landmarks and Time to Objective Progression Showing the *P* Value From Log-Rank Test

Population Landmark	PSA Decline	N	%	Median (days)	*P* (log-rank)
Combined					
6 weeks	All	346			.0027
	Decline	50	14	170	
	No decline	296	86	88	
9 weeks	All	278			< .0001
	Decline	85	31	183	
	No decline	193	69	96	
12 weeks	All	209			< .0001
	Decline	80	38	193	
	No decline	129	62	122	
Suramin					
6 weeks	All	175			.0662
	Decline	41	23	170	
	No decline	134	77	99	
9 weeks	All	153			.0052
	Decline	59	39	176	
	No decline	94	61	106	
12 weeks	All	118			.0002
	Decline	53	45	193	
	No decline	65	55	121	
Placebo					
6 weeks	All	171			.0582
	Decline	9	05	260	
	No decline	162	95	86	
9 weeks	All	125			.0021
	Decline	26	21	193	
	No decline	99	79	88	
12 weeks	All	91			.0374
	Decline	27	30	193	
	No decline	64	70	123	

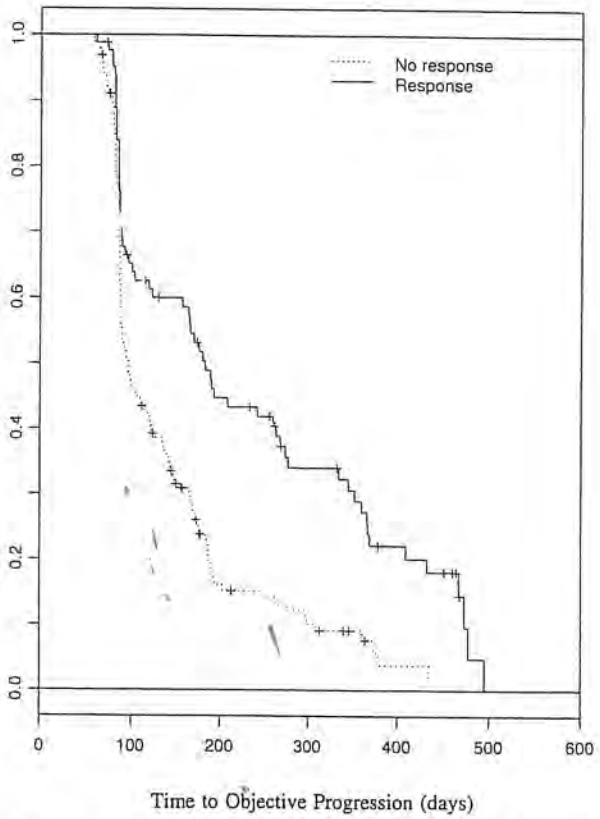

Fig 2. Time to objective progression by PSA decline at 9-week landmark (all patients). Median (days): response = 183 days; no response = 96 days (*P* < .0001.

relationship between PSA decline and OPFS (data not shown). In a multivariate analysis, PSA decline remained predictive of median OPFS at all three landmarks for the combined population, and at the 9- and 12-week landmarks for the suramin and placebo groups (Table 3). A PSA decline in the suramin-treated group was associated with an improvement in median OPFS at the 9-week landmark (hazards ratio, 1.62; $P = .03$) and at the 12-week landmark (hazards ratio, 2.36; $P = .001$). As an example, progression-free survival of all patients as a function of PSA decline with a 9-week landmark is shown in Fig 2.

Association of PSA Decline With TTPP

A decline in PSA was associated with improved median TTPP in the entire cohort at all three landmarks (358 days *v* 184 days at the 6-week landmark, $P = .00269$; 428 *v* 189 days at the 9-week landmark, $P = .0009$; and 428 *v* 185 days at the 12-week landmark, $P = .0131$). In the suramin group, a decline in PSA was also associated with an improved median TTPP at all three landmarks (358 days *v* 269 days at 6 weeks, $P = .0208$; 392 days *v* 184 days at 9 weeks, $P = .0038$; and 392 days *v* 184 days at 12 weeks, $P = .0208$). No association between PSA decline and median TTPP was observed in the placebo group (Table 5). All potential confounders were included in the multivariate analysis. In a multivariate analysis, a PSA decline remained predictive of median TTPP at all three landmarks for the entire group and the suramin-treated group, with hazards ratios between 1.72 and 2.41 for the entire group and a hazards ratio of approximately 2.5 for the suramin group (Table 3). For illustrative purposes, TTPP of all patients as a function of PSA decline using a 9-week landmark is shown in Fig 3.

DISCUSSION

The majority of HRPC patients lack measurable disease, and responses in osseous disease are difficult to quantify. Consequently, clinically relevant end points such as pain control and analgesic use have become more widely used.[15-19]

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