A Phase II Trial of Suramin Monthly × 3 for Hormone-Refractory Prostate Carcinoma

Nicholas J. Vogelzang, M.D.[1]
Theodore Karrison, Ph.D.[2]
Walter M. Stadler, M.D.[1]
Juan Garcia, M.D.[3]
Helene Cohn, R.N.[1]
John Kugler, M.D.[4]
Thomas Troeger, M.D.[3]
Leonard Glannone, M.D.[5]
Rose Arrieta, R.N.[1]
Mark J. Ratain, M.D.[1]
Everett E. Vokes, M.D.[1]

[1] Section of Hematology/Oncology, Department of Medicine, University of Chicago, Chicago, Illinois.

[2] Department of Health Studies, University of Chicago, Chicago, Illinois.

[3] Michiana Hematology/Oncology, South Bend, Indiana.

[4] Oncology/Hematology Association, Peoria, Illinois.

[5] Central Illinois Hematology/Oncology Center, Springfield, Illinois.

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Address for reprints: Nicholas J. Vogelzang, M.D., Fred C. Buffett Professor of Medicine and Director, University of Chicago Cancer Research Center, 5841 S. Maryland Ave., MC 1140, Chicago, IL 60637-1470; Fax: (773) 702-0595; E-mail: nvogelza@medicine.bsd.uchicago.edu

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BACKGROUND. The goal of the current study was to determine the prostate-specific antigen (PSA) and objective response rates and the pharmacokinetics associated with a monthly × 3 one-hour infusion of suramin in 58 patients with hormone-refractory prostate carcinoma.

METHODS. A PSA response was defined as a > 50% reduction in the PSA level from baseline for at least 3 consecutive evaluations over a minimum of 6 weeks. The suramin dose was 2400 mg/m^2 taken intravenously on Day 1, 1620 mg/m^2 on Day 29, and 1292 mg/m^2 on Day 57. All patients received 0.5 mg dexamethasone twice daily.

RESULTS. Among 56 evaluable patients (median entry PSA level, 229.5 ng/mL), there were 21 PSA responders (37.5%). Among 27 patients with measurable disease, there were 5 responders (4 partial and 1 complete). The median overall survival time was 15.3 months. Grade III fatigue (14.1%) was the predominant toxicity observed. Suramin plasma levels remained high even 3 months after treatment was discontinued. Among the 12 evaluable patients who previously had received chemotherapy, the PSA response rate was 42%; one response was observed among 4 patients with measurable disease, and the median survival was 12 months.

CONCLUSIONS. Monthly bolus suramin was well tolerated, reduced PSA levels, and induced objective responses, even in patients who previously had received chemotherapy. *Cancer* **2004;100:65–71.** *© 2003 American Cancer Society.*

KEYWORDS: chemotherapy-refractory prostate carcinoma, monthly suramin, dexamethasone, prostate-specific antigen.

It was estimated that in 2001, approximately 543,000 men worldwide were diagnosed with prostate carcinoma. Although therapy for localized disease cures the large majority of men with prostate carcinoma, metastatic disease still claims the lives of almost 31,000 men per year in the United States.[1] Thus, effective systemic therapy for prostate carcinoma remains a pressing public health need.

Androgen ablation (hormone therapy) has been the most effective systemic treatment method for metastatic or locally advanced prostate carcinoma since 1941, when Huggins et al.[2] reported the first clinical experience with this method. Most patients experience relief of bone pain symptoms, an improved sense of well-being, improved objective findings on bone scan, and a > 95% decrease in prostate-specific antigen (PSA) levels.[3] Unfortunately, most patients with advanced metastatic prostate carcinoma experience clinical progression in spite of castration, after a period of 18–24 months. Secondary hormonal manipulations, including antiandrogen withdrawal and the administration of glucocorticoids, estrogens, ketoconazole, and PC-SPES, can be effective, but *hormone-refractory* prostate carcinoma

(HRPC) commonly progresses, leading to death within 12–15 months.[4]

The benefit of non-hormone-based therapy, including cytotoxic chemotherapy, in this setting is relatively modest. As first reported by Kelly et al.,[5] a decline of 50% in PSA level is a good benchmark for measuring benefit due to chemotherapy. In 5 sequential trials of the Cancer and Leukemia Group B (CALGB) involving megestrol acetate,[6] mitoxantrone plus hydrocortisone,[7] docetaxel plus estramustine and hydrocortisone,[8] ketoconazole plus hydrocortisone,[9] and suramin plus glucocorticoid,[10] decreases of ≥ 50% in PSA level corresponded to radiologic and clinical responses and predicted a nearly doubled median survival time.

Suramin, a polysulfonated aromatic compound first synthesized as an agent against trypanosomiasis and onchocerciasis, has a broad and unusual array of biologic features that have been exploited in cancer therapeutics. Among these features is the ability to bind to receptors of peptide growth factors (e.g., platelet-derived growth factor, transforming growth factor β, epidermal growth factor, and fibroblast growth factor), thereby potentially inhibiting ligand-receptor interactions and tumor proliferation.[11,12] Furthermore, suramin inhibits DNA topoisomerase II and protein kinase C.[13,14] Finally, via endocytosis, suramin enters the lysosome, where it can inhibit glycosaminoglycan (GAG) catabolism. The ensuing accumulation of GAG may also have antiproliferative effects.[15] Clinical trials over the last 10 years have demonstrated the consistent antitumor activity of suramin in prostate carcinoma and several other malignancies.[16–29] The ability of suramin to decrease PSA expression in vitro without inducing cytotoxicity, however, has led many to question its role in treating prostate carcinoma.[22,23]

Suramin has a very long terminal half-life, which resulted in marked variability in measured plasma concentrations when suramin was administered by continuous infusion in the early clinical trials conducted by the National Cancer Institute. This finding led early investigators to explore adaptive control, with feedback dosing to target plasma concentrations of 150–300 μg/mL. The cost, inconvenience, and institutional commitment associated with adaptive control precluded routine use of this cumbersome strategy. Subsequently, several groups reported pharmacokinetic data from fixed-dose regimens that maintained appropriate suramin concentrations without adaptive control.[19,21] At the University of Chicago (Chicago, IL), we developed a fixed-dosing scheme that called for a 1-hour infusion of suramin on Days 1, 29, and 57.[24,25] Due to the long elimination half-life of suramin, doses in the Phase I trial of this regimen were gradually decreased throughout the course of therapy to avoid high peak plasma concentrations. There appeared to be only modest interpatient variability in plasma concentrations and acceptable toxicity, and thus the monthly × 3 schedule was further tested in a Phase II study in patients with progressive prostate carcinoma after castration.

MATERIALS AND METHODS

Study Design

The primary objective of this Phase II study was to determine the PSA and objective response rates associated with suramin administered as a monthly × 3 one-hour infusion in patients with HRPC. Secondary objectives included characterization of the toxicity of monthly suramin, assessment of overall survival rates, and further characterization of the pharmacokinetics of the current suramin schedule.

Eligibility Criteria

Eligibility criteria included: 1) a histologically documented adenocarcinoma of the prostate with progressive systemic disease despite at least 1 endocrine manipulation; 2) a PSA level > 4 ng/mL and documented evidence of progressive disease (if a patient had objectively measurable disease, an elevated PSA level was not required); 3) a performance status of 0, 1, or 2 on the CALGB scale; 4) at least 3 weeks since major surgery or radiotherapy; 5) no prior suramin use and exposure to 2 or fewer chemotherapeutic agents, including estramustine; 6) failure after an adequate trial of antiandrogen withdrawal; 7) absolute neutrophil count > 1500/μL, hemoglobin > 9 g/dL, platelet count > 100,000/μL, prothrombin time ≤ 1.25 × the upper limit of normal (ULN), creatinine < 1.5 × ULN, bilirubin ≤ 1.5 × ULN, and serum glutamic oxaloacetic transaminase ≤ 1.5 × ULN (or ≤ 5 × ULN if increased due to malignancy); 8) no serious medical illnesses that would compromise patient care, no active acute infections, and no history of another malignancy (except for nonmelanomatous skin cancer or Stage Ta bladder carcinoma); and 9) provision of informed consent. The protocol was approved by the human investigations committee (Investigational Review Board) of the University of Chicago and was in accordance with an assurance filed with and approved by the United States Department of Health and Human Services.

Progressive disease on entry was defined as progressive symptoms of bone pain with bone lesions on bone scan or on radiograph; a 25% increase in a measurable disease mass or the appearance of more than 2 new lesions on physical examination or computed tomography (CT) scan; or at least 3 consecutive increases in PSA level, separated by at least 6 weeks,

compared with a baseline value. Patients receiving chronic exogenous corticosteroids were eligible if they had received a stable dose for at least 6 weeks and their PSA levels had increased on at least 2 consecutive measurements over that period.

Treatment Regimen

Suramin was administered once a month for 3 months, with concurrent dexamethasone (0.5 mg twice daily) and fludrocortisone (0.1 mg every morning) treatment to protect against suramin-induced glucocorticoid and mineralocorticoid deficiency.[29–31] The initial suramin dose was 2400 mg/m^2 intravenously infused over 60 minutes. The dosage was tapered to 1620 mg/m^2 for the second month of administration and to 1292 mg/m^2 for the third month. In general, suramin treatment was to be withheld from patients experiencing NCI Common Toxicity Criteria (version 2) Grade III toxicity until the toxicity resolved to Grade I or less. Treatment was discontinued if unacceptable toxicity occurred, if the patient experienced disease progression, or if the patient requested discontinuation. Blood samples for determination of suramin plasma levels were obtained immediately before dosing on Days 1, 29, and 57 and monthly for 3 months thereafter. Suramin plasma levels were determined as reported previously.[24,25] Administration of dexamethasone and fludrocortisone was continued for 1 month after Day 57.

Response Criteria

For all patients with measurable disease (i.e., 1 lesion at least 2 cm in diameter), measurements of tumor size were made by CT scan, bone scan, or magnetic resonance imaging at baseline, at 4 months (i.e., 1 month after the last dose of suramin), and every 3 months thereafter until disease progression occurred. A complete response was defined as the complete disappearance of all evidence of disease, and a partial response was defined as a $\geq$ 50% reduction in the sum of the products of the perpendicular diameters of all measurable masses. Complete and partial responses were to be confirmed by a second evaluation at least 4 weeks later.

Serum PSA levels were determined at baseline and then every 2 weeks for the first 3 months, at 4 months, and every 3 months thereafter. A PSA response was defined as a $\geq$ 50% reduction in PSA level relative to the pretreatment level for at least 3 successive evaluations and for a minimum of 6 weeks from the first documented PSA response. Progressive disease with respect to PSA was defined as at least 2 consecutive increases in the PSA level to $>$ 150% of the baseline level if the baseline level was $>$ 20 ng/mL, or an increase of $\geq$ 200% (i.e., a doubling of the PSA level) if the baseline level was $\leq$ 20 ng/mL. Patients meeting neither criterion by 4 months were identified as having stable disease with respect to PSA. These definitions of PSA response were arrived at after consultation with the medical staff of the National Cancer Institute/Cancer Treatment Evaluation Program (NCI/CTEP). The definitions were formalized before the PSA consensus conference was convened by the NCI/CTEP and before its recommendations were published.[30]

Pain response was not prospectively measured in this study. Thus, the principal investigator (N.J.V.) evaluated pain responses (and was blinded to PSA results) retrospectively. The records of patients treated at the University of Chicago or at Michiana Hematology/Oncology (South Bend, IN) were reviewed using the following post hoc scoring criteria: *definite pain decrease* (discontinuation of narcotics), *mild pain decrease* (one or more notations of decreased pain in the medical record), *no pain change, mild pain increase* (one or more notations of increased pain), and *definite pain increase* (increased pain or new pain on study).

Statistical Methods

The current study used a Simon[31] two-stage design to test the null hypothesis that the true objective/PSA response rate (i.e., the percentage of patients who have *either* a traditional or PSA response) is 15% against the alternative hypothesis that the true response rate is $\geq$ 30%. For an α level of 10% and 90% power, this evaluation required the enrollment of 23 patients in the first stage and the enrollment of an additional 32 patients in the second stage. If 3 or fewer responses were observed among the first 23 patients, the trial was to be terminated. Otherwise, 12 or more responses among all 55 patients would be sufficient to reject the null hypothesis and to declare that further study of the drug was warranted.

Objective tumor response rates (for patients with measurable disease) and PSA response rates (for all patients) were computed, and exact 95% confidence intervals (CIs) were calculated using the binomial distribution. Overall survival rates were estimated using the Kaplan–Meier[32] method, and the median survival time and its associated 95% CI were determined using the method described by Brookmeyer and Crowley.[33] The association between response rate and pain score was assessed using the Fisher exact test. Finally, two-sample t tests were used to compare mean suramin levels between responders and nonresponders.

RESULTS

Fifty-eight patients were entered into the multicenter trial, slightly in excess of the targeted sample size.

TABLE 1
Demographic and Clinical Characteristics

Variable	No. of patients (%)
Median age in yrs (range)	72 (44–86)
Race	
Caucasian	50 (86.2)
Hispanic	1 (1.7)
African American	7 (12.1)
Previous hormone therapy	58 (100)
Previous chemotherapy	13 (22.4)
Mitoxantrone	9 (15.5)
Taxane/vinca class	2 (3.4)
Previous radiotherapy	38 (65.5)
Previous surgery	42 (72.4)
CALGB performance status	
0	19 (32.8)
1	37 (63.8)
2	2 (3.4)

CALGB: Cancer and Leukemia Group B.

Demographic and clinical characteristics are shown in Table 1. The median age at entry was 72 years; 86% of all patients were Caucasian, and 12% were African American. All patients previously had received hormonal therapy, and 13 (22%) had received chemotherapy as well; 9 patients had received at least mitoxantrone, and the remainder had received various other agents. Sixty-five percent of all patients had undergone radiotherapy (either definitive or palliative), and nearly three-quarters had undergone prostatectomy. Only 2 patients (3.4%) entered the trial with a performance status score of 2. The median PSA level at entry was 229.5 ng/mL (range, 69–1736.2 ng/mL).

Regarding the two-stage evaluation criteria, 9 of the 23 patients in the first stage of the study had either a traditional clinical/radiologic or PSA response, as did 22 (39.6%) of the 56 patients total who were evaluable for clinical/radiologic and/or PSA response. Two patients were not evaluable for PSA response; one had no PSA measurements, and the other had only a baseline measurement. Based on these findings, suramin used in the current schedule can be declared sufficiently active to warrant further study. The overall PSA response rate was 37.5% (95% CI, 24.9–51.5%). Among patients with no prior chemotherapy ($n = 45$; 1 patient was not evaluable), the median decrease in PSA level was 67.7%, with 16 of 44 patients (36.4%) achieving a PSA response. Among patients who previously had received chemotherapy ($n = 13$; 1 patient was not evaluable), the median decrease was 58.9%, with 5 of 12 patients (41.7%) achieving a PSA response; 1 of these 5 responders had no previous exposure to glucocorticoids.

Twenty-seven patients had measurable disease; 5 had clinical/radiologic responses (4 partial responses and 1 complete response), yielding an objective response rate of 18.5% (95% CI, 6.3–38.1%). Two of the patients who had partial clinical/radiologic responses also had PSA responses; the other two experienced decreases in PSA level that did not satisfy the definition of a PSA response. The patient who had a complete clinical/radiologic response also had a > 95% decrease in PSA level. Of the four patients with measurable, chemotherapy-refractory disease, one had a partial response.

TABLE 2
Reported Toxicities

Toxicity type	No. of patients evaluated	No. of patients (%) Grade 1	Grade 2	Grade 3
WBC	57	5 (8.8)	3 (5.3)	1 (1.8)
ANC	57	4 (7.0)	0	1 (1.8)
Platelets	56	12 (21.4)	2 (3.6)	0
Hemoglobin	57	31 (54.4)	15 (26.3)	0
Bilirubin	56	2 (3.6)	1 (1.8)	1 (1.8)
Creatinine	56	12 (21.4)	6 (10.7)	0
SGOT	55	6 (10.9)	1 (1.8)	0
SGPT	30	3 (10.0)	0	0
Alkaline phosphatase	55	24 (43.6)	9 (16.4)	4 (7.3)[a]
Fever	56	5 (8.9)	6 (10.7)	0
Neutropenic fever	57	0	0	1 (1.8)
Pain	57	13 (22.8)	15 (26.3)	5 (8.8)
Fatigue	57	25 (43.9)	16 (28.1)	8 (14.1)[a]
Anorexia	57	17 (29.8)	6 (10.5)	3 (5.3)
Nausea	57	15 (26.3)	5 (8.8)	0
Emesis	57	8 (14.0)	1 (1.8)	0
Diarrhea	57	4 (7.0)	1 (1.8)	3 (5.3)
Constipation	57	6 (10.5)	2 (3.5)	0
Oral	57	4 (7.0)	0	2 (3.5)
Skin	57	11 (19.3)	7 (12.3)	1 (1.8)
Infection	57	2 (3.5)	3 (5.3)	1 (1.8)
Neuropathy	57	15 (26.3)	2 (3.5)	0
Respiratory	57	4 (7.0)	7 (12.3)	4 (7.0)
CNS	56	1 (1.8)	0	0
Weight loss	57	4 (7.0)	0	0
Chills	57	1 (1.8)	1 (1.8)	0
Alopecia	57	1 (1.8)	0	0

WBC: white blood cell; ANC: absolute neutrophil count; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvate transaminase; CNS: central nervous system.
[a] Includes one Grade 4 toxicity.

Toxicity data are shown in Table 2. Notable toxicities included Grade III–IV elevated alkaline phosphatase levels ($n = 4$; none had transaminase toxicity or increases in alkaline phosphatase levels during the first course of therapy), Grade III pain ($n = 5$), Grade III–IV fatigue ($n = 8$), and Grade III respiratory problems ($n = 4$). In addition, 5 patients experienced Grade III ($n = 4$) or Grade IV ($n = 1$) edema; the patient with Grade IV edema also had a venous throm-

TABLE 3
Suramin Plasma Concentration Data

Sampling point	No. of patients evaluated	Median (mg/mL)	Range (mg/mL)
Day 29	41	75	29–121
Day 57	38	116	57–196
After month 1	31	119	11–217
After month 2	29	93	49–168
After month 3	21	60	33–120

bosis. Three patients experienced Grade III hyperglycemia.

Pain responses to suramin were evaluated retrospectively in 25 patients. Seven of these patients had no pain before or during treatment, and three patients had no pain but left the study before completion for other reasons. Of the remaining 15 patients who were evaluable for pain response, 3 had definite increases in pain, 1 had no change, 5 had mild decreases, and 6 had definite decreases. One of the six patients with definite decreases in pain had a partial response to treatment. Of the 11 patients who had mild or definite decreases in pain, 4 (36.4%) had PSA responses, compared with none of the 4 patients who had unchanged or increased pain.

Suramin plasma concentration data are summarized in Table 3. As expected, all baseline measurements on Day 1, before the start of therapy, were below the detection level of the assay used to make the measurement. The median plasma concentration increased over the course of treatment, from 75 mg/mL on Day 29 to 116 mg/mL on Day 57 (the last day of suramin therapy). The plasma concentration remained at a high level 1 month after treatment, and at 3 months after the discontinuation of treatment, the median level still was 60 mg/mL. However, there was no significant difference in plasma concentration between patients who achieved PSA responses and those who did not (Table 4).

The Kaplan–Meier survival curve for all 58 patients enrolled in the trial is shown in Figure 1. Survival times ranged from < 1 to > 38 months. The median survival time was 15.3 months (95% CI, 9.8–18.4 months). Eight patients survived longer than 2 years. Among the 13 patients who previously had received chemotherapy, the median survival time was 12 months (95% CI, 6.2–18.4 months); among the 45 who had not previously received chemotherapy, the median survival time was 15.4 months (95% CI, 9.5–19.4 months).

TABLE 4
Comparison of Suramin Concentrations (Prostate-Specific Antigen Responders versus Prostate-Specific Antigen Nonresponders)

	PSA responders		PSA nonresponders		
Sampling point	No. of patients evaluated	Mean ± SE (mg/mL)	No. of patients evaluated	Mean ± SE (mg/mL)	*P* value
Day 29	13	79 ± 5	28	71 ± 4	0.23
Day 57	16	117 ± 6	22	114 ± 6	0.73
After month 1	14	127 ± 9	17	119 ± 11	0.57
After month 2	14	97 ± 7	15	92 ± 9	0.72
After month 3	11	68 ± 6	10	59 ± 9	0.38

PSA: prostate-specific antigen; SE: standard error.

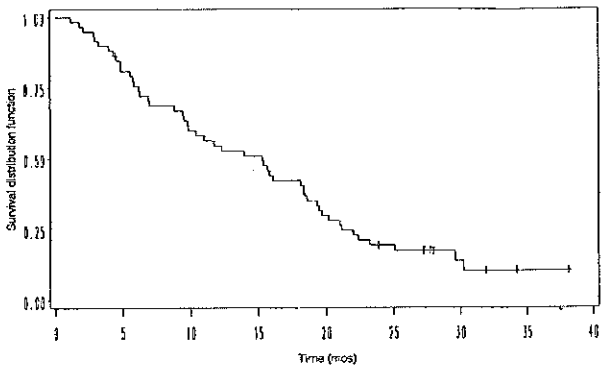

FIGURE 1. Survival after the administration of monthly bolus suramin.

DISCUSSION

Any role for suramin plus a glucocorticoid for use as first-line treatment for HRPC effectively ended when the Oncology Advisory Panel of the Food and Drug Administration (FDA) voted against approval of suramin for that indication.[29] In retrospect, the cumbersome schedule, the pleotropic toxicities, and the modest efficacy associated with suramin all played a part in the drug's failure to win approval. Yet in the ensuing years, only modest progress has been made in the treatment of HRPC. In contrast to breast carcinoma, nonsmall cell lung carcinoma, and colon carcinoma, for which agents have been approved as second- and even third-line therapy, no new agent has been approved by the FDA as first- or second-line therapy for prostate carcinoma that has progressed despite castrate levels of testosterone. The results of the current study, in which 42% (5 of 12) of evaluable patients who previously had received chemotherapy experienced PSA responses, should be considered in that context.

The observed PSA responses to the current schedule of suramin were similar in frequency (37.5%) to the

responses observed in previous Phase III studies of suramin[10,27] and to the responses associated with the FDA-approved regimen of mitoxantrone plus a glucocorticoid.[7] PSA, objective, and pain responses also were observed in patients with prior exposure to chemotherapy (predominantly mitoxantrone).

The relatively low objective response rate associated with the current regimen (18.5%) is somewhat similar to the rate observed with mitoxantrone plus prednisone (7%) and may reflect the relative drug resistance of soft-tissue HRPC lesions. Recently, Small et al.[34] demonstrated that the survival of patients with measurable soft-tissue disease is statistically significantly shorter than the survival of patients with only bone disease. The molecular basis for the more aggressive behavior of HRPC lesions in nonbone organs is unclear.

It also is possible that the rate of response to the suramin/dexamethasone combination results entirely from the dexamethasone component. Glucocorticoids have a small but measurable effect on prostate carcinoma that has progressed after castration. Among glucocorticoid-naive patients, the PSA response rate ranges from 5 to 20%.[7,27] It is not clear what the PSA and measurable disease response rates are when glucocorticoids are reinstituted after previous exposure to them. Both the type of glucocorticoid used and the duration of previous exposure may influence response. Thus, the five observed PSA responses to suramin plus dexamethasone among patients previously exposed to chemotherapy probably can be attributed to the newly introduced agent, suramin.

Monthly suramin was well tolerated, although Grade III fatigue was observed in approximately 15% of patients. Fatigue is a poorly characterized entity that commonly accompanies progressive disease but frequently is associated with anemia. Forty-six of the 57 evaluable patients had mild-to-moderate (Grade I–II) anemia (median nadir hemoglobin level, 11.1 g/dL) due to suramin; this finding suggests a link between anemia and fatigue in the current study. Erythropoietin use was uncommon in the current cohort, although two patients did receive red blood cell transfusions during suramin therapy. The mechanisms of suramin-induced fatigue and anemia are unclear, but such toxicities may also result from the progression of prostate carcinoma.

In conclusion, the suramin regimen used in the current study is safe, easy to administer, and relatively effective in treating both chemotherapy-naive and chemotherapy-pretreated patients. Calvo et al.[28] made similar observations. With the finding of a median survival of 15.3 months (12 months in patients who previously had received chemotherapy), the role of suramin as a second-line chemotherapeutic agent for the treatment of HRPC should, perhaps, be reevaluated. It also may be worthwhile to pursue suramin analogues.

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