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Suramin's development: what did we learn?

Maninderjeet Kaur[1], Eddie Reed[2], Oliver Sartor[3], William Dahut[1] and William D. Figg[1]
[1]*Molecular Pharmacology Section, Cancer Therapeutic Branch, Center for Cancer Research, National Cancer Institute, National Institute of Health, Bethesda, MD;* [2]*Mary Babb Randolph Cancer Center, West Virginia University, Morgantown, WV;* [3]*Stanley Scott Cancer Center, Louisiana State University, New Orleans, LA, USA*

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Summary

Suramin, a polysulphonated napthylurea, has been extensively evaluated over the past 10 years as an anticancer agent, with the most interest in the treatment of prostate cancer. Early clinical results were promising with response rates of up to 70% being reported. However, a recent double-blind study showed only modest palliative effect in patients with androgen independent prostate cancer. In retrospect, it appears those initial reports failed to control for confounding variables such as antiandrogen withdrawal and hydrocortisone.

Suramin causes numerous reversible toxicities (lethargy, rash, fatigue, anemia, hyperglycemia, hypocalcemia, coagulopathies, neutropenia, renal and hepatic complications). Neurotoxicity has been the most significant complication and appears to be related to the intensity of the dosing regimen. An optimal therapeutic dose has not been determined, but it is clear that adaptive controls add little benefit.

Aside from moderate toxicities and the low therapeutic index in patients with prostate cancer, suramin's development has taught us some valuable lessons (i.e., anti-androgen withdrawal was noted during suramin's development, the use of PSA as an indicator of tumor burden was initiated during the evaluation of suramin). These lessons can be applied to all clinical trials in hormone refractory prostate cancer. Suramin has significantly enhanced the evolution of our knowledge in several areas of prostate cancer biology and treatment.

Introduction

Suramin, a polysulphonated napthylurea, was first synthesized in 1916 by Bayer AG [1]. It was noted to have trypanocidal activity and thus became the drug of choice for African trypanosomas and onchocerchiasis [2,3]. In 1979, suramin was noted to inhibit reverse transcriptase and thus was evaluated in various clinical trials in patients with Acquired Immunodeficiency Syndrome (AIDS) [4,5]. Although these clinical trials showed minimal activity against human immunodeficiency virus (HIV), the drug seemed promising in HIV associated neoplasms such as: Kaposi's Sarcoma and Non-Hodgkins lymphoma [3]. On a molecular level, suramin has the ability to block the actions of various growth factors such as; fibroblast growth factors (FGF), platelet derived growth factors (PDGF), transforming growth factors alpha and beta (TGF), and insulin like growth factor I (IGFI) [6,7,8,9]. Suramin has also been shown to be a strong inhibitor of angiogenesis. Other biological activities of suramin are similar to polyanionic glycosaminoglycans and heparinioids [7]. Preclinical data showed *in vitro* antiproliferative activity against human prostate cancer cell lines (LNCaP, PC-3, and DU145) [8–10]. Therefore, suramin was evaluated for antineoplastic properties with emphasis in patients with prostate cancer.

Suramin as a single agent in metastatic prostate cancer

Initial trials used a continuous infusion of suramin and targeted concentration between 100–350 μg/ml [8,9]. Subsequently, it was felt that concentration below 100 μg/ml showed no significant biological

activity and above 350 μg/ml significant neurotoxicity was reported [9,10]. In addition, increased inter- and intra-patient pharmacokinetic variability was observed which resulted in several studies using adaptive control [9,10]. At this point, preliminary data suggested meaningful activity against prostate cancer.

In 1992, a phase II trial conducted at the NCI evaluated efficacy and dosing schedule of suramin [8]. This trial enrolled 38 patients with androgen-independent prostate cancer (AIPC) and used continuous infusion to reach a peak concentration of 300 μg/ml at the end of two weeks. An eight week wash out period was given to recover from toxicity. Subsequent cycles were repeated. In 17 patients with measurable soft tissue disease, three patients exhibited complete response, three showed partial response, and five patients had prostate specific antigen (PSA) decline of 75% or more [11]. In the remaining 21 patients with bone metastasis, only eight patients showed PSA decreases of $\geq$ 75% and PSA levels normalized ($<$ 4.0 ng/ml) in five other patients. Figure 1 shows the difference in survival between those patients that had at least a 50% decline in PSA and those that did not. A four week landmark analysis revealed that the median survival was 21.1 months for those patients with a $\geq$ 50% decline in PSA compared with 6.8 months for those patients with a $<$ 50% decline in PSA.

Subsequently, a phase I trial at University of Maryland Cancer Center was conducted which utilized short intermittent infusion using adaptive control with feedback to maintain plasma drug concentrations between 150–250, 175–275, or 200–300 μg/ml in three different cohorts [12]. These investigators reported that 77% of patients had 50% or more decline in PSA and 55% of patients had a reduction of 75% or more in PSA. Eighty three percent (83%) of patients experienced reduction in pain. The method of dosing suramin utilizing adaptive control is cumbersome and time consuming and was not clinically feasible on a large scale [12]. Therefore, Kobayashi and colleagues evaluated the activity of intermittent dosing of suramin using a fixed dose regimen (N=63) [13]. They recommended that on the first day a dose of 1440 mg/m^2 be used in future trials with gradual decrease in dosing on days 2, 8, and 9 of a 4 week cycle [13]. These studies stressed the need for determining the optimal drug concentration range and duration of therapy, and the role of required therapeutic monitoring [13].

In 1995 Panchivan et al. analyzed five different trials of suramin in AIPC and concluded that the overall response was 55% in regards to PSA declines of 50% or more and 30% in regards to measurable disease [14]. This combined response rate is lower than initial reports, but still appeared promising.

A more recent double-blind, randomized, phase III trial comparing suramin plus hydrocortisone (n=288 patients) vs. placebo plus hydrocortisone (n=230 patients) found a statistically significant palliative advantage for those treated with suramin [15]. The palliative advantage was shown by decrease in pain and/or decrease in opiod analgesic use and prolongation of pain response. The toxicities in this study were mild to moderate and easily medically manageable. Rash was the most common toxicity followed by asthenia, edema, nausea and vomiting. In addition, the PSA declined in 32% of patients receiving suramin vs. 16% of patients in the placebo arm [15]. However, the survival was similar in both study groups. Compared to initial high response rates reported with suramin, this study was disappointing. In fact, the low response rate coupled with no survival advantages, plus the problems of toxicity resulted in the recommendation of not approving suramin for marketing by an FDA advisory committee.

PSA: can we rely on it?

PSA, 34 kilodalton protein, is found in prostatic tissue and in seminal fluid [16]. Serum PSA values reflect prostate volume in both malignant and benign tissue and has been an essential tool in the diagnosis of prostate cancer [14,17,18]. In 1987 Ferro et al. utilized PSA as a marker of tumor burden in a phase II trial in AIPC patients [19]. Subsequently, PSA reduction of 50% or more have been reported by several groups to be associated with survival advantage [11,20]. However, Thalmann et al. in 1996 reported that suramin had a differentiating effect on tumor growth and PSA expression in LNCaP cells (androgen dependent cell line) as well as in C4-2 cells (androgen independent cell line grown *in vitro*) [17]. They suggested that PSA values might not be an appropriate end point in clinical trials using suramin therapy in AIPC because declines in PSA might not be associated with tumor regression. This type of observation was confirmed both clinically and pre-clinically with other compounds, such as CAI [21,22]. However, it should be pointed out that the effects of suramin on PSA expression have been mixed; some investigators have reported no effect on PSA expression [23]. Eisenberger et al. demonstrated the need for prospective clinical data by examining

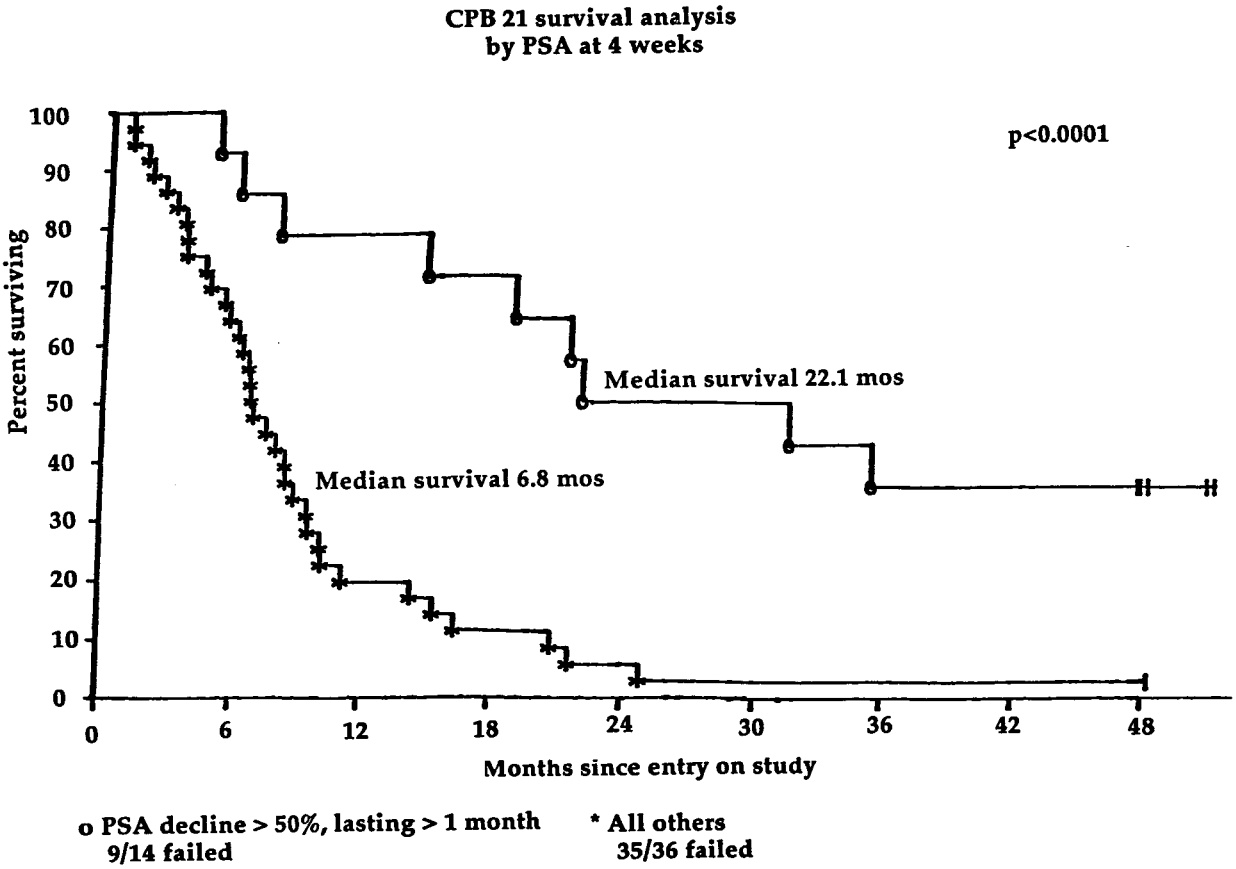

Figure 1. Survival of patients with ≥ 50% PSA decline versus less than 50% PSA decline at 4 week after suramin treatment.

the significance of PSA changes and reported a therapeutic benefit of suramin in patients with prostate cancer who had decline in PSA [20]. Likewise the data presented in Figure 1 confirms those observations. Nonetheless, when compared with Eisenberger's data, Small and colleagues [15] found a higher percent of patients treated with suramin had a PSA decline, but no difference in survival when compared to placebo.

Controlling for confounding variables

Various other trials confirmed activity of suramin against prostate cancer with variable response rates (Table 1). In 1993 Scher and colleagues made a key observation about the antitumor activity of discontinuing flutamide (Table 2) [24]. This maneuver was confirmed by other groups to have activity in 20–30% of AIPC patients [25]. In addition, a survival benefit was shown to be associated with cessation of flutamide [26]. This observation led to speculation of the impact of confounding variables such as flutamide withdrawal and hydrocortisone coadministration on previously reported studies evaluating suramin's activity.

Often patients discontinued their antiandrogen immediately before starting suramin. Because of the adrenal ablation associated with suramin, replacement doses of hydrocortisone were necessary to prevent adrenal insufficiency. Many patients received higher than replacement doses of hydrocortisone in the trials for treatment of rashes, etc. Corticosteriods alone may have palliative or objective response in AIPC [27]. Tannock et al. [27,29] reported response rates between 13.6 and 38% with 7.5–10 mg/day of prednisone. Likewise, Sartor et al. found a 33% response rate with prednisone [30].

In 1995 a group at the NCI prospectively evaluated the activity of suramin while controlling for both the hydrocortisone variable and flutamide withdrawal in 54 patients with AIPC [31]. Figure 2 shows schema of patient distribution and response [31]. This trial re-

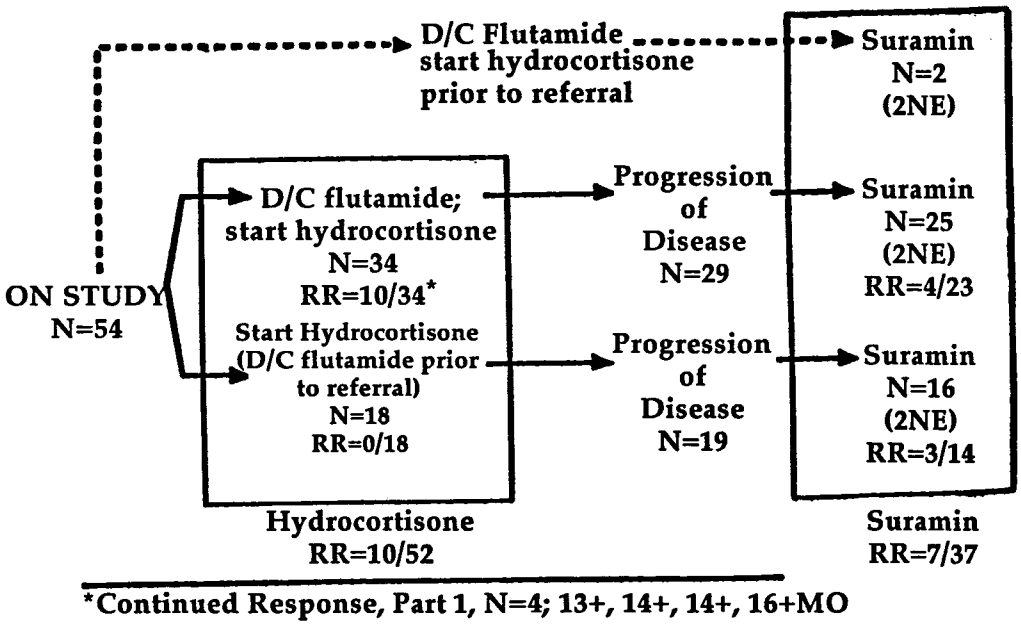

Figure 2. Schema, entry of patients and response (> 50% PSA decline) to hydrocortisone and suramin therapies. N: number; D/C: discontinue; RR: response rate; NE: not evaluable; MO: months.

Table 1. Response rates with suramin in clinical trials

Trials	PSA % response rate		Objective Response rate CR + PR	Subjective Response rate (pain relief)	Dosing
	≥ 50%	≥ 75%			
Eisenberger et al. [33]	24/31 (77%)	17/31 (55%)	6/12 (50%)	24/31 (83%)	Fixed, intermittent, and adaptive control
Kobayshi et al. [13]	9/12 (75%)	4/12 (33%)	1/7 (14%)	NR	Fixed and intermittent
Eisenberger et al. [33]	45/67 (67%)	NR	7/18 (40%)	18/37 (49%)	Fixed, intermittent, and adaptive control
Reyno et al. [53]	24/36 (67%)	18/36 (50%)	0/4 (0%)	12/23 (52%)	Fixed
Rosen et al. [27]	16/32 (50%)	7/32 (22%)	2/20 (10%)	22/32 (69%)	Fixed, intermittent, and adaptive control
Myers et al. [10]	13/38 (34%)	21/38 (55%)	6/17 (35%)	15/21 (71%)	CIVI
Garcia-Schürmann et al. [40]	7/27 (26%)	NR	Bone scan 2/27 (7.4%)	1/10 (10%)	CIVI, fixed, and adaptive control
Dawson et al. [31]	7/37 (19%)	NR	NR	NR	Fixed, intermittent, and adaptive control
Kelly et al. [32]	5/28 (18%)	NR	0/28 (0%)	NR	Fixed and intermittent
Bowden et al. [50]	13/75 (17.3%)	NR	NR	NR	CIVI and adaptive control

CR = complete response, and PR = partial response based on the National Prostatic Cancer Project (NPCP) criteria. NR = not reported. CIVI = continuous infusion

Table 2. Flutamide withdrawal response rates alone and in combination with suramin

Study authors	Therapy	No. of patients	Response	
			> 50% decline in PSA	Median response duration (mo.)
			Flutamide withdrawal alone	
Figg WD et al. [25]	FW	21	33.3%	4.7
Scher HI et al. [24]	FW	35	29%	5
Srinivas S et al. [51]	FW	82	15%	3
Herrada J et al. [52]	FW	41	28.2%	3.2
			Suramin at the time of flutamide withdrawal	
Bowden C et al. [50]	FW+SUR	7	85%	NA
Dawson N et al. [31]	FW+SUR	25	44%	2.5

FW = flutamide withdrawal; HC = hydrocoftisone; SUR = suramin

ported response rate of 19% for suramin (based on a $\geq$ 50% decline in PSA) with a median duration of 2.2 months. Later that year Kelly et al. reported the results from a similar trial in which they controlled for flutamide withdrawal and hydrocortisone [32]. The response rate was 18%, based on $\geq$ 50% decline in PSA; no measurable response was reported. The low response rate of suramin was in agreement with Rosen et al., who also controlled for flutamide withdrawal [27].

In contrast, Eisenberger and colleagues retrospectively evaluated their database, controlling for flutamide withdrawal [33]. They concluded that no significant relationship existed between the PSA decline associated with response and prior flutamide withdrawal [33]. They reported a decline in PSA of 50% or more in 67% of their patients. Again, however, three prospective trials support the theory that simultaneous flutamide withdrawal could account for much of suramin's activity.

Flutamide withdrawal and combination chemotherapy

In another non-randomized trial, the combination of suramin plus aminoglutethimide was evaluated with or without simultaneous flutamide withdrawal [34]. The authors noted a partial response rate of 14.2% when flutamide had been discontinued prior to initiation of suramin, and aminoglutethimide, whereas a 44% partial response rate was reported for the cohort in which suramin therapy was begun concomitant with antiandrogen withdrawal. Median survival (21.9 vs. 14.2 months) and progression free survival at one year (27.1% vs. 19.8%) were also better in the simultaneous antiandrogen withdrawal group. In addition, two other non-randomized observations support this hypothesis [35]. These data suggest that suramin plus aminoglutethimide increases the response rate associated with antiandrogen withdrawal; a theory which should be prospectively evaluated in future clinical trials.

Activity in patients with androgen dependent disease

Dawson et al. combined suramin (target plasma concentration of 175–300 μg/ml) and hydrocortisone with leuprolide (an LHRH agonist) and flutamide in previously untreated metastatic prostate cancer patients (N=50) [36]. An overall response rate of 67% was reported, combining complete and partial responses. Figure 3 depicts the overall survival in this population (update August 1999). The median survival was 3.4 years. Although this was not a randomized trial, and the patient population evaluated had a poor prognosis (D1 and D2 stage), this survival data seems promising. Nonetheless, Hussain et al. have recently reported on 62 previously untreated metastatic patients that receive combined androgen blockade plus four cycles of suramin [37]. The cycles were separated by 6 months and the treatment regimen was an aggressive fixed dose schedule. Fifty-four percent (54%) of patients had significant toxicity to suramin, with one drug toxicity related death. Furthermore, the response rate was not overly impressive (progression free survival was 14 months, CI 10 to 19 months)

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