

# Phase I Study of Low-Dose Suramin as a Chemosensitizer in Patients with Advanced Non-Small Cell Lung Cancer<sup>1</sup>

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## ABSTRACT

**Purpose:** Our preclinical studies have shown that acidic and basic fibroblastic growth factors confer broad spectrum chemoresistance and that low concentrations (10–50  $\mu\text{M}$ ) of suramin, a nonspecific fibroblastic growth factor inhibitor, enhance the antitumor activity of paclitaxel *in vivo*. The present Phase I study evaluated low-dose suramin in combination with paclitaxel/carboplatin in advanced non-small cell lung cancer patients.

**Experimental Design:** Patients received suramin followed by paclitaxel (175–200 mg/m<sup>2</sup>) and carboplatin area under the concentration-time curve of 6 mg/ml/min, every 3 weeks. The initial suramin dose for the first cycle was 240 mg/m<sup>2</sup>, and the doses for subsequent cycles were calculated based on the 72-h pretreatment plasma concentrations. The recommended suramin dose would yield plasma concentrations of 10–20  $\mu\text{M}$  at 48 h in  $\geq 5$  of 6 patients.

**Results:** Fifteen patients (11 stage IV, 4 stage IIIB, 9 chemo-naive, and 6 previously treated) received 85 courses. The most common toxicities were neutropenia, nausea/vomiting, malaise/fatigue, and peripheral neuropathy. No treatment-related hospitalizations, adrenal dysfunction, or episodes of sepsis occurred. The initial suramin dose resulted in the targeted concentrations of 10–20  $\mu\text{M}$  at 48 h in 5 of the first 6 patients treated but also resulted in peak concentrations > 50  $\mu\text{M}$  in all patients. Dividing the suramin dose to

be administered in two doses, 24 h apart, yielded the target concentrations and avoided undesirable peak concentrations. Discernable antitumor activity occurred in 7 of 10 patients with measurable disease, including 2 with prior chemotherapy. The median time to tumor progression is 8.5 months (range, 3–27+ months) for 12 evaluable patients.

**Conclusions:** Low-dose suramin does not increase the toxicity of paclitaxel/carboplatin combination. The suramin dose can be calculated based on clinical parameters. Because of the preliminary antitumor activity observed, efficacy studies in chemo-naive and chemorefractory patients are under way.

## INTRODUCTION

The polysulfonated naphthylurea suramin, an agent originally developed for the treatment of parasitic infestations (1–4), has long been a subject of interest as a candidate antitumor agent. Suramin inhibits reverse transcriptase in RNA tumor viruses (5), mitochondrial oxidative enzymes (6, 7), and the binding of growth factors to their respective receptors. The affected growth factors include platelet derived growth factor (8), epidermal growth factor (9, 10), vascular endothelial growth factor (11), transforming growth factor  $\beta$  (12), insulin-like growth factor 1 (13, 14), and FGFs<sup>3</sup> (15–18). Suramin also inhibits the activity of protein kinase C isoforms (19).

Suramin has shown concentration-dependent antiproliferative activity *in vitro* against cultured tumor cells and explanted human tumor specimens including colon, endometrium, kidney, non-small cell lung, and ovarian carcinoma, as well as malignant glioma, melanoma, and mesothelioma (20–23). However, at concentrations  $\leq 50 \mu\text{M}$ , minimal antiproliferative activity was observed and several studies have shown growth stimulation of some tumor cells at these low suramin concentrations (22–26).

On the basis of these earlier preclinical findings, most studies evaluating suramin as a cytotoxic agent in humans have targeted concentrations of  $\geq 200 \mu\text{M}$ . At these doses, suramin appears to have modest to moderate antitumor activity in hormone refractory prostate carcinoma (27–30), marginal activity in recurrent high-grade gliomas (31), and no or insignificant activity in non-small cell lung (32), breast (32), colorectal, (33) and renal carcinomas (34). Although careful clinical study has led to a strategy to circumvent its seemingly unpredictable pharmacokinetic behavior (35–37), a protean spectrum of toxicities including polyneuropathy (38), adrenal insufficiency (39), skin and appendages alterations (40–43), coagulopathy

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<sup>3</sup> The abbreviations used are: FGF, fibroblast growth factor; ACTH, adrenocorticotropic hormone; AUC, area-under plasma concentration-time curve; DLT, dose-limiting toxicity; NSCLC, non-small cell lung cancer; PR, partial response; TTP, time to tumor progression.

(44, 45), and renal insufficiency (46) has limited its development as an anticancer agent. The onset of severe neurological toxicity (sensory motor axonal and progressively disabling demyelinating neuropathy) is generally associated with steady-state plasma concentrations of  $\geq 275 \mu\text{M}$  (47–49).

In contrast to the high concentrations required for antiproliferative activity, inhibition of growth factor binding to receptors by suramin occurs at substantially lower concentrations. For example, basic FGF, a growth factor that has been implicated in neovascularization and tumor growth (18, 50), is inhibited at suramin concentrations  $< 50 \mu\text{M}$  (51).

Au *et al.* (51, 52) recently reported that elevated levels of acidic FGF and basic FGF in solid and metastatic tumors confer broad spectrum resistance to chemotherapy drugs with diverse structures and mechanisms of action and that low concentrations of suramin that are devoid of antitumor activity reverse the FGF-induced chemoresistance *in vitro*. In addition, in mice with well-established lung metastases, low and nontoxic doses of suramin (10 mg/kg, twice weekly  $\times$  3 weeks), yielding plasma concentrations of between 10 and 20  $\mu\text{M}$ , enhanced the antitumor effect of paclitaxel; the combination resulted in tumor eradication in 42% of animals (none in the single agent paclitaxel group), a 9-fold greater reduction of the density of nonapoptotic cells and a 30% increase in the apoptotic cell fraction (53).

On the basis of the synergy of paclitaxel and low-dose suramin demonstrated in the preclinical studies and the observation that low-dose suramin had no or minimal toxicity in patients, we designed the present Phase I trial of low-dose suramin in combination with paclitaxel/carboplatin in patients with advanced NSCLC. The principal objectives of the study were to: (a) determine the dose of suramin that, when given in combination with commonly used doses of the paclitaxel/carboplatin regimen, would result in plasma concentrations of 10–20  $\mu\text{M}$  (14–29  $\mu\text{g/ml}$ ) at 72 h (later adjusted to 48 h); (b) characterize the principal toxicities of the combination; and (c) seek preliminary evidence of antitumor activity.

## MATERIALS AND METHODS

**Eligibility.** Patients with histologically confirmed stage IV NSCLC or patients with stage IIIB disease (not amenable to curative-intent radiation and chemotherapy) were eligible for this study. Eligibility criteria also included: (a) age,  $\geq 18$  years; (b) Eastern Cooperative Oncology Group performance status of 0–2 (ambulatory and capable of self care); (c) a life expectancy  $\geq 3$  months; (d) treatment with no more than one prior chemotherapy regimen; (e) no cytotoxic chemotherapy agents for at least 28 days; (f) adequate hematopoietic (WBC count  $\geq 3,000/\mu\text{l}$ , absolute neutrophil count of  $\geq 1,500/\mu\text{l}$ , platelets  $\geq 100,000/\mu\text{l}$ , and hemoglobin level of  $\geq 9.0 \text{ g/dl}$ ); hepatic (total serum bilirubin level  $< 1.5$  times institutional upper normal limits, aspartate amino transaminase and alanine amino transaminase  $< 2.5$  times upper normal limits); and renal functions (serum creatinine  $< 1.5 \text{ mg/dl}$  or calculated creatinine clearance  $\geq 50 \text{ ml/min}$ ); (g) no brain metastases or leptomeningeal disease, unless the lesions had been previously irradiated, not being treated with corticosteroids, and were stable and asymptomatic; (h) no history of myocardial infarction within the

previous 6 months, congestive heart failure requiring therapy, or unstable angina; (i) no known active serious infectious process or current treatment for HIV type 1 infection; (j) no uncontrolled diabetes mellitus; (k) no history of hypersensitivity to Cremophor EL; (l) baseline-corrected serum calcium of  $\leq 11.5 \text{ mg/dl}$ ; and (m) no  $\geq$  grade 2 neuropathy. The treatment protocol and informed consent were approved by the Cancer Therapy Evaluation Program at the National Cancer Institute and the institutional review board at The Ohio State University. Patients gave written informed consent according to federal and institutional guidelines before treatment.

**Dosage and Dose Escalation.** The carboplatin dose was calculated using the Calvert equation (54) to yield an AUC of 6 mg/ml/min and remained fixed throughout the study. The starting dose of paclitaxel was 175 mg/m<sup>2</sup>. The starting doses of paclitaxel and carboplatin were considered to be the minimal effective doses for the combination in the treatment of NSCLC. The initial suramin dose of suramin was 240 mg/m<sup>2</sup> given on day 1 and was calculated to yield target concentrations of 10–20  $\mu\text{M}$  at 72 h (later changed to 48 h) after infusion; these target concentrations were selected based on the preclinical data (53). Treatment was repeated every 3 weeks. Subsequent treatment doses for paclitaxel and carboplatin were based on toxicity encountered during the prior cycle. Subsequent treatment doses of suramin were modified based on the residual suramin plasma concentrations at 72 h before treatment. Intrasubject dose escalation for paclitaxel and carboplatin was not permitted.

Modification of the starting doses of suramin in subsequent cohorts of at least three patients was to be performed if pharmacokinetic analyses of suramin plasma concentrations were off-target in  $\geq 2$  of the first 6 patients treated. The dose of paclitaxel was to be increased to 200 mg/m<sup>2</sup> in a subsequent cohort of at least 3 patients, once the target dose of suramin was defined, as long as DLTs did not occur in  $\geq 2$  of the first 6 patients during their first course of treatment. Paclitaxel was to be reduced to 135 mg/m<sup>2</sup> if treatment resulted in DLT in  $\geq 2$  of these patients.

Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0 (55). DLT was defined as one of the following: (a) an absolute neutrophil count  $< 500/\mu\text{l}$  for  $> 5$  days or associated with any grade 2 fever (temperature,  $\geq 38.5^\circ\text{C}$ ); (b) a platelet count  $< 10,000/\mu\text{l}$ ; (c) grade 3 nonhematological toxicity (including diarrhea, nausea, and vomiting) that resulted in interruption of treatment for  $> 2$  weeks; or (d) any grade 4 nonhematological toxicity. The recommended dose level was defined as the suramin dose that in combination with the highest tolerated dose of paclitaxel and carboplatin at an AUC of 6 resulted in concentrations of 10–20  $\mu\text{M}$  at 72 h (later changed to 48 h) after infusion.

**Drug Administration.** Suramin was supplied by the National Cancer Institute, Division of Cancer Treatment and Diagnosis, as sterile, 600-mg, 10-ml vials. The vials were reconstituted with sterile water, resulting in a 100 mg/ml solution. The desired dose was additionally diluted in 0.9% sodium chloride or 5% dextrose in water. Commercially available paclitaxel (Taxol; Bristol Myers Squibb) was obtained from the hospital pharmacy in 30 (5 ml), 100 (16.7 ml), and 300 mg (5 ml) vials and was prepared according to the manufacturer's directions in glass or polyolefin containers diluted in 500–1000

ml of 5% dextrose or 0.9% sodium chloride. Commercially available carboplatin (Paraplatin; Bristol Myers Squibb) was obtained from the hospital pharmacy as sterile single-dose vials containing 50, 150, and 450 mg. The content of each vial was reconstituted with either sterile water, 5% dextrose in water, or 0.9% sodium chloride to produce concentrations of 10 mg/ml.

All three drugs were administered by i.v. infusion, using an infusion pump. Suramin was administered over 30 min, followed by paclitaxel over 3 h, and carboplatin over 1 h. Standard premedication included oral dexamethasone (20 mg 12 and 6 h before paclitaxel), diphenhydramine (50 mg i.v.), famotidine (20 mg i.v.), and ondansetron 16 mg p.o. given 30 min before paclitaxel.

**Pretreatment Assessment and Follow-Up Studies.** Histories, physical examinations, and routine laboratory studies were performed pretreatment and preceding each course of treatment. Routine laboratory studies included serum electrolytes, chemistries, and complete blood cell counts with differential white cell counts. Complete blood cell counts were also performed weekly, and blood clotting times, urinalysis, pregnancy tests (when indicated), chest radiographies, and electrocardiograms were performed before initiating treatment. If patients developed toxicity manifested by grade 3–4 abnormalities in hematological or biochemical laboratory parameters, the tests were repeated immediately and then daily until the toxicity resolved. Tumors were measured after every other course, and treatment was continued in the absence of progressive disease or intolerable toxicity. The RECIST criteria for response evaluation (56) was used to define objective responses, although measurable disease was not required to be eligible to participate in this trial. A complete response was defined as the disappearance of all target and nontarget lesions. A PR required at least a 30% reduction in the sum of the longest diameter of target lesions compared with pretreatment measures, and progressive disease required an increase of at least 20% in the sum of the longest diameter of target lesions. Objective responses required confirmation by a subsequent response evaluation separated by at least 4 weeks.

To evaluate if potential alterations in the adrenal axis are induced by the low dose suramin used in this study, as has been previously reported for higher doses (39), ACTH stimulation tests were performed pretreatment and after every three courses for patients remaining on treatment. Patients received 0.25 mg ACTH<sub>1–24</sub> (cosyntropin) i.m. or i.v., and samples for cortisol levels were obtained immediately before cosyntropin injection and 30 min after injection. To avoid potential interference with the test results caused by the oral dexamethasone premedication required before paclitaxel, ACTH stimulation tests were performed on day 15 of the cycle (*i.e.*, 2 weeks after dexamethasone).

**Blood Sampling and Analysis.** Blood samples were obtained from a site contralateral to the drug infusion during the first course of treatment. On treatment days 1 and 2, plasma samples (10 ml) were collected in heparin-containing vacutainer glass tubes before suramin treatment and at 1.5, 2.5, 3.5, 4, 4.5, 6, 9, 12, 15, 24, 48, and 72 h from the beginning of the suramin infusion. In addition, for subsequent courses, samples were obtained 72 h before treatment (to evaluate residual suramin concentrations), 1 h before the start of the suramin infusion, at the end of paclitaxel infusion, at the end of carboplatin infusion, as well as at 24, 48, and 72 h from the beginning of the suramin

Table 1 Patient characteristics

|  | No. of patients |
|--|-----------------|
| Patients treated/toxicity evaluable                    | 15/15           |
| Activity evaluable                                     | 12              |
| Male   | 10              |
| Female   | 5               |
| Median age (range), yr                                 | 62 (42–77)      |
| Eastern Cooperative Oncology Group performance status: |                 |
| 0  | 4               |
| 1  | 8               |
| 2  | 3               |
| Stage  |                 |
| IIIb (malignant pleural effusion)                      | 4               |
| IV   | 11              |
| Previous radiotherapy                                  | 5               |
| Previous chemotherapy                                  |                 |
| None   | 9               |
| One regimen  | 6               |

infusion. Plasma concentrations of suramin were determined using high performance liquid chromatography, as described previously (57).

## RESULTS

**General.** Fifteen patients received 85 courses (median number of courses, 6; range, 1–10) of suramin in combination with paclitaxel and carboplatin. Patient characteristics are listed in Table 1. Nine patients had no prior chemotherapy, whereas 6 patients had received one prior chemotherapy regimen. Five patients had received prior radiation treatment, including a patient previously irradiated for brain metastases. All patients were evaluable for toxicity. Three patients were taken off study early during the first course (within the first week); one individual because of a severe reaction to paclitaxel (did not receive carboplatin), a second subject because of spinal cord compression requiring immediate spine irradiation, and the third because of a revised pathological diagnosis to small cell lung cancer.

The number of new and total patients, courses, and rates of DLTs, per dose level, are listed in Table 2. The starting doses were suramin 240 mg/m<sup>2</sup>, paclitaxel 175 mg/m<sup>2</sup>, and carboplatin at an AUC of 6. At this dose, only 1 of the first 6 patients developed DLT (severe hypersensitivity reaction to paclitaxel). As described below, the final dose of suramin was calculated based on clinical parameters and was administered in two doses 24 h apart. At this new suramin dosing schedule, no DLTs were observed in the next 6 patients, including the 3 patients that received 200 mg/m<sup>2</sup> paclitaxel.

**Pharmacokinetics of Low-Dose Suramin.** Fig. 1 shows the plasma concentration-time profiles of suramin during the first cycle of treatment. Table 3 depicts the suramin plasma concentrations at the target time points. The target suramin concentration range of between 10 and 20 μM at 72 h was attained in 5 of 6 patients (range, 10–16 μM). However, peak concentrations of suramin attained at 1.5 h exceeded 50 μM in all patients (range, 56–97 μM), and concentrations attained immediately after paclitaxel infusion exceeded 50 μM in 5 of 6 patients (11 of 19 treatment courses).

Because of concerns of possible interference with the an-

Table 2 Dose escalation scheme

| Suramin initial (mg/m <sup>2</sup> ) <sup>a</sup> | Dose level paclitaxel (mg/m <sup>2</sup> ) | Carboplatin AUC (mg/ml/min) <sup>a</sup> | No. of patients |                      |       | Total courses | New patients with DLT/ total new patients <sup>b</sup> |
|---|--|--|-----------------|----------------------|-------|---------------|--|
|   |  |  | New             | Reduced to this dose | Total |               |  |
| 240 d1  | 175  | 6  | 6               | 0                    | 6     | 19            | 1/6  |
| 160 d1, 80 d2                                     | 175  | 6  | 3               | 6                    | 9     | 38            | 0/3  |
| 160 d1, 80 d2                                     | 200  | 6  | 3               | 0                    | 3     | 15            | 0/3  |
| Individualized                                    | 200  | 6  | 3               | 0                    | 3     | 13            | 0/3  |
| Total   |  |  | 15              |                      |       | 85            |  |

<sup>a</sup> Suramin doses for second and subsequent courses were calculated based on the 72-h pretreatment plasma concentrations.

<sup>b</sup> First or second course.

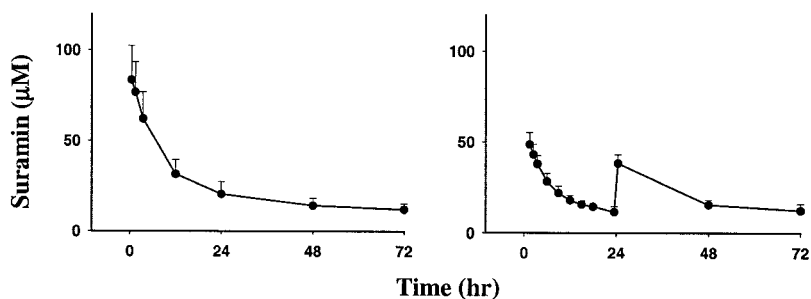


Fig. 1 Suramin plasma concentration-time profiles. Suramin was given by single dose (left panel, total of 19 treatments) or by split doses (right panel, total of 66 treatments) as described in "Materials and Methods" and "Results." Data are mean  $\pm$  SD. Data points are connected by straight lines.

titumor effect of paclitaxel because of potential cell cycle arrest by  $>50 \mu\text{M}$  suramin, the treatment protocol was amended to split the administration of suramin during the first and subsequent treatment cycles, for current and subsequent patients, into two separate doses given 24 h apart; two-thirds of the dose on day 1 (before paclitaxel), and the remaining one-third on day 2 (24 h from first infusion). In addition, we found that the AUCs for paclitaxel and carboplatin attained in the first 48 h constituted  $>92$  and  $>99\%$  of their respective total AUCs (unpublished data). Hence, the doses of suramin for all subsequent and new treatments were revised to attain the target concentrations of  $10\text{--}20 \mu\text{M}$  at 48 h instead of 72 h.

This new suramin dosing schedule yielded the targeted suramin concentrations of  $10\text{--}20 \mu\text{M}$  at 48 h in all 66 treatments. The peak suramin concentrations exceeded  $50 \mu\text{M}$  in only 2 of 6 patients (55 and  $59 \mu\text{M}$ ); this occurred only during the first treatment cycle that used a higher loading suramin dose and did not occur during the subsequent cycles that used lower suramin doses.

Because of its slow elimination, significant residual plasma concentrations deriving from the previous suramin dose were detected 72 h before the administration of the subsequent doses in all patients (Table 3). Hence, it was necessary to adjust the suramin dose for the subsequent treatments and to maintain the plasma levels within the narrow ranges required by this study. Furthermore, to eliminate the need of real-time pharmacokinetics in future studies, we derived an empirical equation to calculate the suramin dose.<sup>4</sup> This equation, depicted below, was

derived using population pharmacokinetic analysis of the data of the first 12 patients and was tested in three additional patients: suramin dose in mg = FACTOR  $\times$  (absolute value of body surface area, without units)<sup>2</sup>. The value of the FACTOR was calculated based on the target suramin concentration (set at  $15 \mu\text{M}$  at 48 h) and the volume of distribution and elimination rate constant of suramin. FACTOR equaled 110 divided by  $(e^{-k} \times t)$ .  $k$  is the elimination rate constant and  $t$  is time. The results in the first 12 patients showed a 15% lower elimination rate constant in women ( $n = 3$ ) compared with men ( $n = 9$ ;  $0.0022 \text{ h}^{-1}$  versus  $0.0026 \text{ h}^{-1}$ ). Accordingly, the numerical values of FACTOR were lower for women.

For the first dose, FACTOR was calculated to be 125 for males and 123 for females. For the ease of dose calculation, the value of FACTOR was set at 125 for both genders. To attain the same target concentrations of  $15 \mu\text{M}$  at 48 h during subsequent treatment cycles, the dose administered during a subsequent cycle should replace the fraction of the dose that was eliminated during the interval between treatments. Hence, the value of FACTOR equaled the product of  $125 \times \text{BSA}^2 \times (1 - e^{-k} \times t)$ . Note that in contrast to the first cycle where  $t$  equaled 48 h, the value of  $t$  during subsequent cycles is a variable that equals the time lapsed since the previous cycle.

We evaluated the above suramin dose calculation method in 3 additional patients. The results showed that in all 13 treatments, the target concentration range of  $10\text{--}20 \mu\text{M}$  at 48 h was attained, and the peak suramin concentration did not exceed  $50 \mu\text{M}$  (Table 3).

**Hematological Toxicity.** Table 4 lists the number of courses associated with neutropenia, anemia, and thrombocytopenia. Overall, moderate to severe neutropenia was frequent. Grade 3 and 4 neutropenia occurred in 31 (36%) and 30 courses (35%), respectively. However, grade 4 neutropenia was in all

<sup>4</sup> D. Chen, S. Song, J. L.-S. Au, T. K. Yeh, M. Villalona-Calero, G. A. Otterson, S. Kanter, A. J. Murgo, M. Grever, and M. G. Wientjes. Pharmacokinetics of low dose suramin as a chemosensitizer in patients, manuscript in preparation.



Table 3 Plasma concentrations of suramin at target time points

| Patient ID <sup>a</sup> | No. of treatments | Suramin (μM) <sup>a</sup>                  |                                       |   |   |   |
|-------------------------|-------------------|--|---------------------------------------|---|---|---|
|                         |                   | At 1.5 h after initiating suramin infusion | Immediately after paclitaxel infusion | At 48 h after initiating suramin infusion | At 72 h after initiating suramin infusion | At 72 h before the next suramin treatment |
| Single dose             |                   |  |                                       |   |   |   |
| 1                       | 1 <sup>b</sup>    | 89.2                                       | 77.4                                  | 18.6                                      | 15.6                                      | NM <sup>c</sup>                           |
| 2                       | 5                 | 97.2                                       | 40.9–77.5                             | 19.3                                      | 9.9–15.0                                  | 2.0–5.0                                   |
| 3                       | 5                 | 64.0                                       | 40.5–63.2                             | 11.4                                      | 9.4–13.1                                  | 3.0–4.5                                   |
| 4                       | 1 <sup>b</sup>    | 55.7                                       | 46.9                                  | 9.9                                       | 8.3                                       | 2.0                                       |
| 5                       | 4                 | 87.4                                       | 54.6–76.2                             | 11.0                                      | 10.2–13.2                                 | 3.2–5.1                                   |
| 6                       | 3                 | 67.3                                       | 45.1–52.0                             | 15.2                                      | 13.9–19.1                                 | 5.0–6.0                                   |
| Split dose              |                   |  |                                       |   |   |   |
| 2                       | 1                 | NM <sup>c</sup>                            | 31.3                                  | 13.7                                      | NM  | NM  |
| 3                       | 5                 | NM   | 24.0–32.3                             | 12.4–17.7                                 | 11.5–13.0                                 | 4.8–6.7                                   |
| 5                       | 6                 | NM   | 33.2–48.2                             | 13.9–17.6                                 | 13.6–14.4                                 | 2.9–5.0                                   |
| 6                       | 7                 | NM   | 27.1–37.1                             | 14.4–20.4                                 | 13.3–14.7                                 | 5.0–6.0                                   |
| 7                       | 4                 | 55.5                                       | 30.4–42.4                             | 14.7–18.1                                 | NM  | 3.8–6.7                                   |
| 8                       | 10                | 59.9                                       | 23.4–45.3                             | 10.4–20.7                                 | 7.8–14.9                                  | 4.6–7.9                                   |
| 9                       | 4                 | 48.7                                       | 29.3–38.8                             | 14.7–15.5                                 | 12.4                                      | 2.7–4.0                                   |
| 10                      | 4                 | 43.6                                       | 28.6–37.8                             | 15.3–17.8                                 | 12.6–15.4                                 | 3.7–5.4                                   |
| 11                      | 6                 | 48.4                                       | 27.7–38.2                             | 13.5–17.5                                 | 10.7–14.8                                 | 2.7–4.6                                   |
| 12                      | 6                 | 48.3                                       | 28.8–39.0                             | 10.3–21.3                                 | 10.2–18.7                                 | 3.4–6.4                                   |
| 13                      | 6                 | 37.0                                       | 21.5–28.9                             | 10.2–13.9                                 | 7.3–9.5                                   | 2.4–3.6                                   |
| 14                      | 6                 | 49.5                                       | 22.0–37.3                             | 12.9–15.6                                 | 10.3–13.9                                 | 3.5–5.4                                   |
| 15                      | 1 <sup>b</sup>    | 47.9                                       | 36.0                                  | 19.4                                      | 16.3                                      | NM  |

<sup>a</sup> Plasma samples were obtained on various times during first and subsequent treatment courses. Some samples (*e.g.*, 1.5-h postsuramin) were obtained only during the first treatment for the single dose schedule, whereas the other samples (*e.g.*, postpaclitaxel and 72-h postsuramin) were obtained during some or all treatments. The 48-h postsuramin samples were obtained during the first treatment in the single dose schedule and during all treatments in the split dose schedule. For the time points where samples were obtained during multiple treatments, the ranges of concentrations attained in different treatments are shown.

<sup>b</sup> Patients 1, 4, and 15 received only 1 treatment.

<sup>c</sup> NM, not measured.

Table 4 Toxicities of low-dose suramin with paclitaxel/carboplatin

| Toxicity <sup>a</sup>    | No. of courses with grade |    |    |    |    |
|--------------------------|---------------------------|----|----|----|----|
|                          | 0                         | 1  | 2  | 3  | 4  |
| Hematologic              |                           |    |    |    |    |
| Neutropenia <sup>b</sup> | 14                        |    | 10 | 31 | 30 |
| Anemia <sup>b</sup>      | 66                        |    | 16 | 3  | 0  |
| Thrombocytopenia         | 60                        | 12 | 7  | 6  | 0  |
| Non-hematologic          |                           |    |    |    |    |
| Nausea/vomiting          | 26                        | 36 | 22 | 1  | 0  |
| Asthenia/fatigue         | 21                        | 19 | 32 | 13 |    |
| Peripheral neuropathy    | 57                        | 19 | 8  | 1  |    |
| Myalgias/arthralgias     | 33                        | 47 | 5  | 0  |    |
| Hypersensitivity/rash    | 63                        | 15 | 6  | 1  | 0  |
| Diarrhea                 | 70                        | 14 | 0  | 1  | 0  |

<sup>a</sup> Toxicities are reported for all courses.

<sup>b</sup> Grade 1 neutropenia (absolute neutrophil count, 1500–1999/ml) and grade 1 anemia (hemoglobin, 10–11.9 g/dl) are not reported because they were permitted at study entry and re-treatment.

instances of short duration (<5 days) and never associated with fever. There were no episodes of grade 4 anemia or thrombocytopenia, and three and six courses were associated with grade 3 anemia and thrombocytopenia, respectively. These episodes were seldom clinically significant, requiring platelets and RBC transfusions in only two and one courses, respectively. No dose delays attributable to neutropenia or anemia occurred, and only

2 patients (a total of three courses) required dose delays because of thrombocytopenia. Overall, the observed hematological toxicities appeared no different from those expected from the paclitaxel/carboplatin combination.

**Nonhematological Toxicity.** The principal nonhematological toxicities of the combination are listed according to severity in Table 4. The most common nonhematological effects were nausea, vomiting, asthenia (fatigue, malaise), peripheral neuropathy, myalgias/arthralgias, hypersensitivity, and diarrhea.

Nausea and/or vomiting occurred frequently. However, these effects were generally mild to moderate; 36 (42%), 22 (26%), and 1 (1%) courses were associated with grades 1, 2, or 3 nausea and/or vomiting, respectively. All patients received prophylactic antiemetic treatment *p.o.* with a 5HT<sub>3</sub> serotonin antagonist. Asthenia/fatigue/malaise were reported by 14 patients during 64 treatment courses. Although the contribution of therapy to this constellation of symptoms is hard to establish in patients with advanced malignancies, the transiency of the highest grade of these symptoms (*i.e.*, improving during the third week of each cycle) and its association with higher cumulative doses (10 of 13 episodes of grade 3 toxicity during a third or later course) indicate a possible relationship.

Neuropathy was generally mild to moderate, with grade 3 symptoms occurring in only 1 patient that developed spinal cord compression from metastatic disease to the spine, within 2 days after receiving the first course of treatment. Five of eight epi-

Table 5 Antineoplastic Activity

| Dose level<br>paclitaxel/carboplatin<br>(mg/m <sup>2</sup> /d)/<br>(AUC, mg/ml/min) | No. of<br>courses | Stage | Metastatic sites                                 | Prior therapy                             | Best response <sup>a</sup> | Time to<br>tumor<br>progression<br>(mo) |
|---|-------------------|-------|--|---|----------------------------|---|
| 175/6   | 6                 | IIIB  | Pleura   | Pleurodesis/cisplatin-XRT                 | SD (NM)                    | >27                                     |
|   | 10                | IV    | Adrenal glands/mediastinum/<br>paraspinal muscle | Lobectomy                                 | PR                         | 18                                      |
|   | 10                | IV    | Pericardium, lungs, bones                        | None                                      | PR                         | 8                                       |
|   | 10                | IV    | Chest wall/mediastinum                           | None                                      | PR                         | 10                                      |
|   | 4                 | IIIB  | Mediastinum                                      | None                                      | PR                         | 7.5                                     |
|   | 6                 | IIIB  | Pleura   | None                                      | SD (NM)                    | 13                                      |
| 200/6   | 10                | IV    | Liver/bones                                      | Paclitaxel/oxaliplatin                    | MR                         | 9                                       |
|   | 4                 | IV    | Sternal mass/multiple lungs                      | XRT/cisplatin; paclitaxel/<br>carboplatin | PR                         | 3                                       |
|   | 4                 | IV    | Lungs multiple/brain                             | Lobectomy/brain XRT                       | SD                         | 5                                       |
|   | 6                 | IV    | Pleura/multiple lungs                            | Lobectomy/XRT; Wedge<br>resection         | SD                         | 10                                      |
|   | 6                 | IIIB  | Pleura/lungs (two masses)                        | None                                      | PR                         | 7                                       |
|   | 6                 | IV    | Lungs multiple/liver                             | XRT, vinorelbine                          | SD                         | 6                                       |

<sup>a</sup> XRT, radiation; PD, progressive disease; SD, stable disease; MR, minor response (15%); NM, nonmeasurable.

sodes of grade 2 toxicity occurred after three cycles of treatment with the combination and were characterized by painful dysesthesias of upper or lower extremities (five episodes) or decreases in motor strength in lower extremities (three episodes). Overall, these effects appeared no different from those expected from the paclitaxel/carboplatin combination. Similarly, myalgias and arthralgias commonly associated with paclitaxel were observed in 52 treatment courses.

Hypersensitivity reactions were observed during 22 courses. The most severe reaction occurred in a 67-year-old female with NSCLC metastatic to the mediastinum, bones, and adrenal gland, who had previously received treatment with paclitaxel (four courses) but had no history of idiosyncratic reaction to this agent. The patient had known coronary artery disease. Two and one-half hours into the paclitaxel infusion, the patient developed restlessness and some respiratory wheezing, which initially cleared spontaneously, allowing the paclitaxel infusion to finish. However, respiratory distress and loud wheezes, as well as chest discomfort, confusion, and increases in blood pressure, developed at the end of the infusion. The symptoms improved with sublingual nitroglycerine, i.v. hydrocortisone, and diphenhydramine. The confusion resolved the following morning. Because of safety concerns, the patient was removed from the trial, and a challenge with paclitaxel was not performed. Other episodes of hypersensitivity were mild and characterized by fascial flushing and/or erythematous rashes in face and upper extremities, which resolved without therapy. Mild to moderate nonhematological toxicities observed also included diarrhea, mucositis, and alopecia.

No clinical symptoms indicative of adrenal insufficiency were noted. In addition, ACTH stimulation tests were performed pretreatment in all patients, during course 3 in 10 patients, during course 6 in 7 patients, and in 2 subjects during a ninth or later course of treatment. No significant differences were observed between changes in cortisol levels after ACTH at baseline (mean  $\pm$  SD = 12.9  $\pm$  4.4  $\mu$ g/dl) and after three cycles (11.1  $\pm$  3.6;  $P$  = 0.33, paired  $t$  test) or between baseline and six cycles (10.6  $\pm$  5.9) of treatment ( $P$  = 0.30).

**Antitumor Activity.** Relevant details pertaining to the antitumor effects of the combination in all 15 patients who participated in the study are depicted in Table 5. Twelve patients are evaluable for antitumor activity. Among these 12 patients, 10 had measurable disease and 2 had no measurable disease (metastatic disease to pleura). However, TTP data are available for all 12 patients. The remaining 3 nonevaluable patients were either withdrawn from the study within the first few days (severe reaction to paclitaxel in one patient and need for emergency radiation in the other) or were disqualified (1 patient because of a revised pathological diagnosis from NSCLC to small cell lung cancer. Treatment in the latter patient was changed after the second course to a more conventional small cell lung cancer regimen (*i.e.*, etoposide and cisplatin), resulting in a complete response to treatment.

Seven of 10 patients with measurable disease experienced discernable antitumor activity. These include 6 patients who met the definition of PR as prospectively defined in this trial (RECIST Criteria). One additional patient, who progressed after two courses of paclitaxel/oxaliplatin and had metastases to liver and bones, experienced a 15% overall decrease in the sum of the longest diameter of measurable tumoral lesions (liver and lung) after eight courses of therapy. Tumor progression was demonstrated after two additional courses (overall TTP, 9 months). The 6 patients with PR included a previously surgically resected patient who develop biopsy proven recurrence to the adrenal glands, mediastinum, and paraspinal muscles. The treatment in this patient was discontinued after 10 cycles to receive radiation to the paraspinal muscle area, which was the only positron emission tomography avid and biopsy proven area of residual disease (adrenal gland was negative on rebiopsy) after treatment. Tumor progression (by positron emission tomography) did not occur until 18 months from initiation of the suramin/paclitaxel/carboplatin treatment. For all 12 evaluable patients, the median time to tumor progression is 8.5 months, and 1 patient (no measurable disease) does not have evidence of tumor after 27+ months follow-up.

## DISCUSSION

The severity of the toxicities observed with suramin at the high concentrations required for antitumor activity has limited the development of this drug as a cytotoxic agent. The present study represents a novel approach to use low concentrations of suramin as a chemosensitizer. This is based on the preclinical observation that low-dose suramin, presumably by reversing the FGF-induced chemoresistance, potentiates the antitumor activity of chemotherapy in human xenograft tumors in mice (48–50).

To simulate the preclinical conditions, we targeted a narrow range for the trough and peak concentrations of suramin (10–50  $\mu\text{M}$ ), instead of the maximally tolerated doses typically targeted in Phase I trials. The results of this study show that at the range of targeted concentrations, low-dose suramin did not add to the toxicity profile of the paclitaxel/carboplatin combination (58, 59) and had no interference with the hypothalamic-pituitary-adrenal axis, although 33% of evaluable patients (4 of 12) received the relatively high number of 10 treatment cycles.

The present study successfully identified the suramin dose yielding a target plasma concentration range between 10 and 50  $\mu\text{M}$  over the duration when paclitaxel and carboplatin were present at therapeutically significant levels. As described in detail in a separate study,<sup>4</sup> the relationships between suramin pharmacokinetic parameters and physiological parameters were used in conjunction with population pharmacokinetic analysis to establish an empirical equation that calculates the suramin dose needed to deliver the target concentrations. Results of the last 3 patients whose suramin dose was derived using this equation suggest the applicability of this equation. Additional studies in a larger patient population to confirm the predictive power of this equation are ongoing.

Most of the earlier pharmacokinetic studies of high-dose suramin were conducted in male patients with hormone refractory prostate cancer. The present study included 5 female patients, 3 of whom provided sufficient data for analysis of pharmacokinetic parameters. A preliminary analysis of the results suggests a slower elimination in female patients. These results need to be interpreted carefully because of the small number of female patients in the present study. Additional pharmacokinetic studies in patients with advanced metastatic breast cancer are under way.

Although the concept that optimal biological doses for molecularly targeted agents can be different from their maximally tolerated doses is not new, very seldom are clinical trials designed to have as their major end point the determination of the optimal biological dose. In many instances, this is because of the lack of reliable surrogates of biological activity, the rapid degradation in plasma of the targeted enzymes/proteins, and/or the difficulty of obtaining repetitive tumor samples. The present study used plasma concentrations of suramin as a surrogate biological end point because these concentrations were associated with the reversal of FGF-induced chemoresistance *in vitro* and had demonstrated synergy with chemotherapeutic agents such as doxorubicin and paclitaxel against human xenograft tumors *in vivo* (48–50). The relevance of such a design is that given the lack of toxicity or antitumor activity of single agent suramin at these concentrations, if increased antitumor activity

is demonstrated in subsequent efficacy trials, this trial may set a new paradigm for the design of Phase I clinical trials of biological agents.

In the present trial, we were very mindful of avoiding peak concentrations of suramin that were substantially  $>50 \mu\text{M}$ . This concern arose from studies showing cell cycle perturbations by suramin. Suramin at  $>50 \mu\text{M}$  concentrations causes cell cycle arrest in the  $G_1$  phase for human prostate tumor cells, NIH3T3 cells, and human neuroblastoma cells (60–63). In addition, arrest in the  $G_2$ -M phase for human breast and ovarian tumor cells and arrest in the  $G_2$ -M and S phases for meningioma cells have been reported (64–66). Likewise, preliminary results from our laboratory indicate that suramin at concentrations  $> 50 \mu\text{M}$  arrested human PC3 cells in  $G_1$  phase, whereas lower concentrations did not produce cell cycle perturbations and that high suramin doses yielding  $\sim 200 \mu\text{M}$  plasma concentrations reduced the cell cycle progression in xenograft tumors, whereas low suramin doses yielding  $<50 \mu\text{M}$  concentrations did not (unpublished results). Although it is unclear if maintaining concentrations above these levels for a short period of time would result in antagonistic effects in humans, the concentrations resulting from low-dose suramin in our Phase I study were highly predictable, and the dose can be easily calculated in the clinical setting. Therefore, until careful evaluation of the clinical value of the concept discussed here is completed, it is our recommendation that efficacy trials should aim for the concentrations targeted in the present study.

Although it is beyond the purpose of a Phase I trial, it is of interest to comment on the antitumor activity observed. Despite the few patients and the potential bias introduced by patient selection that may exist in this small group of patients, encouraging antitumor activity was observed in both chemonaïve and previously treated patients. Two observations are noteworthy. First, antitumor activity was observed in 2 patients who had tumor progression after paclitaxel treatment. Second, the median TTP was an impressive 8.5 months, including 2 patients with  $\geq 18$  months before tumor progression was documented. These observations would encourage additional evaluation of low-dose suramin as a chemosensitizer not only in chemonaïve patients in which the median TTP is typically 3–4 months (67) but also in chemorefractory patients. As is the case for most biological agents, TTP or progression-free rate at a particular time interval should be an important part of the analysis of such evaluations.

In summary, low-dose suramin can be combined with commonly administered doses of paclitaxel and carboplatin in NSCLC patients without an increase in toxicity, and the suramin concentration can be predicted based on clinical parameters. The preliminary antitumor activity observed encourages evaluation of the combination in efficacy trials.

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