EDITORIALS

Suramin: Here to Stay!?*

Howard I. Scher*

Suramin was one of the first chemotherapeutic agents developed with efficacy against a parasitic disease. Originally synthesized in the early 1900s, the drug was extensively used in the 1920s and 1930s. Clinical use waned until in vitro studies showed that suramin could inhibit reverse transcriptase and antagonize the binding of a number of polypeptide growth factor ligands (platelet-derived growth factor, basic fibroblast growth factor, transforming growth factor-β, and epidermal growth factor) with their receptors. Demonstration of antitumor activity in hormone-refractory prostatic cancer, a disease for which there is no effective therapy, generated even more interest in the compound.

The highly charged nature of suramin results in a significant degree of protein binding, a factor that may contribute to its diverse biologic actions. Suramin not only affects interactions between growth factor and growth factor receptors—it can also induce differentiation (1) and inhibit mitochondrial function (2), adrenal steroidogenesis (3), protein kinase C (4), glycolysis (5), membrane-associated ion pumps (6), and the metastatic process through an effect on cell motility (7). The effects are nonspecific, and currently, it is unclear whether the tumoricidal action is the result of the extracellular or the intracellular effects of the compound.

Suramin was evaluated in prostatic cancer on the basis of the inhibitory effects on growth-factor-induced mitogenesis and proliferation and antitumor activity against human-derived prostatic cancer cell lines in vitro and in vivo (8). The initial report by Myers et al. (8) in 1989 showed measurable disease response in four of eight patients and prostate-specific antigen (PSA) declines in seven of 11 patients treated. In that trial, suramin was administered by continuous infusion until a target concentration of 280-300 μg/mL was reached. Due to the effects on the adrenal gland, all patients received hydrocortisone replacement from the start of treatment.

While the reported therapeutic efficacy stimulated intense interest, the drug also achieved notoriety for its seemingly prohibitive toxic effects profile. The situation was not dissimilar to that observed with the earliest use of cisplatin. Some toxic effects, such as the skin rash, are idiosyncratic (9), while others, such as the vortex keratopathy, and coagulopathy, are related to the inhibitory effects of suramin on glycosaminoglycan synthesis (10,11). Other side effects include renal insufficiency, adrenal insufficiency, thrombocytopenia, hepatitis, and an increased incidence of infection despite normal blood counts. The most feared complication is peripheral neuropathy, which can progress to a Guillain-Barré syndrome (12).

Based on early National Cancer Institute (NCI) results, confirmatory trials at Memorial Sloan-Kettering Cancer Center, M. D. Anderson Cancer Center, and the Mayo Clinic were initiated. Proportionally, fewer patients responded to the drug. The results, using a variety of dosing regimens, are summarized in Table 1.

Why, then, were investigators so persistent? First, those of us who treat prostatic cancer recognize the importance of not discarding a drug with potential activity. Second, despite fewer responses in some series, some of the responses lasted for more than 1 year, a phenomenon rarely observed in hormone-refractory disease. Third, other investigations were observing responses with different schedules (Table 1). These developments generated an intensive series of investigations to improve the therapeutic index of the compound.

In vitro, the antitumor effect of suramin is dependent on both the concentration of the drug and the time of exposure. Further, a pharmacokinetics evaluation (13) of the first six patients treated at Memorial Sloan-Kettering Cancer Center revealed significant interpatient variability. These observations, coupled with the postulated therapeutic window (see below), led to the design of schedules in collaboration with the University of Maryland that maintain plasma concentrations in a defined range for prolonged durations. In this issue of the Journal, Eisenberger et al. (14) present the first report of the University of Maryland experience.

The study by Eisenberger et al. (14) represents an enormous effort by a closely integrated team of medical oncologists, pharmacologists, pharmacokineticists, research nurses, technicians, and data managers. Here is their treatment schema: A population-based pharmacokinetics profile is derived first. A new patient is then treated, and plasma concentrations are determined both before and after each drug treatment. With the use of a high-speed computer, these concentrations are combined with the population-based model to estimate the pharmacokinetics for the patient. A dosing recommendation is then given. The process is repeated on each day of therapy. As more plasma concentrations are determined, the pharmacokinetic estimates are updated. After the five daily treatments in week 1, steady state is approached, the time to decline to the desired trough level is estimated, and the patient is asked to return on that particular day. Thus, the schedule is flexible both with respect to the amount of drug administered and to the timing of the administration. This process is extremely labor intensive for both the patient and the treating team. Their efforts appear to be justified, though, because the results in prostatic cancer showed measurable disease regression in six of 12 patients (50%; 95% confidence interval = 22%-78%); 24 of 31 patients (77%; 95% confidence interval = 63%-92%) had a greater than 50% decline in PSA from

*See "Notes" section following "References."
A "placebo" effect is likewise possible. Antitumor activity, were observed in less than 10% of patients treated with bone-seeking radioisotopes, while PSA declines, indicative of palliation in up to 60% of patients treated with low-dose prednisone. The contribution of hydrocortisone to the improved pain relief and antitumor effect may be significant. Similarly, we have observed pain palliation in up to 60% of patients treated with bone-seeking radioisotopes, while PSA declines, indicative of antitumor activity, were observed in less than 10% of patients (20). A "placebo" effect is likewise possible.

An alternative trial design is the use of posttherapy declines in PSA. This design is based on the observation that response and survival correlate with changes in PSA after androgen ablation as primary therapy (21). Although the criteria for response in hormone-refractory disease have not been standardized (16), a significant proportion of patients showed a greater than 50% and a greater than 80% decline in PSA from baseline (Table 1). Caution is required, since suramin may inhibit PSA release without killing cells (22). Further, Harland and Duchesne (25) showed that hydrocortisone alone produced posttherapy declines in PSA in over 50% of patients. This demonstration again raises questions as to the role of hydrocortisone. An additional factor, not fully controlled in this trial, is the contribution of flutamide withdrawal to the observed response proportions (24). In this syndrome, some patients treated with combined androgen blockade (orchiectomy or a gonadotrophin-releasing hormone analogue plus flutamide) will respond to the selective discontinuation of flutamide. Thus, prior to entry on trial, we require documentation of progressive disease off flutamide.

Table 1. Summary of results of suramin trials*

<table>
<thead>
<tr>
<th>Center†</th>
<th>Reference No.</th>
<th>Schedule</th>
<th>Measurable disease</th>
<th>Prostate-specific antigen (&gt;50% decrease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI (Bethesda, Md.)</td>
<td>(25)</td>
<td>Infusion‡</td>
<td>17</td>
<td>6 (35%)</td>
</tr>
<tr>
<td>University of Arizona (Tucson)</td>
<td>(25)</td>
<td>Infusion‡</td>
<td>15</td>
<td>7 (47%)</td>
</tr>
<tr>
<td>MSKCC, MDACC, and Mayo Clinic</td>
<td>(36)</td>
<td>Infusion§</td>
<td>36</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Walter Reed Army Hospital (Washington, D.C.)</td>
<td>(37)</td>
<td>Infusion‡</td>
<td>NR</td>
<td>20</td>
</tr>
<tr>
<td>Brussels (Belgium)</td>
<td>(38)</td>
<td>Infusion§</td>
<td>NR</td>
<td>9</td>
</tr>
<tr>
<td>Gustave Roussy (Villejuif, France)</td>
<td>(39)</td>
<td>Infusion§</td>
<td>NR</td>
<td>5</td>
</tr>
<tr>
<td>South Africa</td>
<td>(40)</td>
<td>Infusion‡</td>
<td>25</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>University of Maryland (Baltimore)</td>
<td>(14)</td>
<td>Infusion§</td>
<td>NR</td>
<td>31</td>
</tr>
<tr>
<td>MSKCC</td>
<td>(41)</td>
<td>Cohort A§</td>
<td>9</td>
<td>1 (11%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cohort B§</td>
<td>5</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>131</td>
<td>35 (27%)</td>
</tr>
</tbody>
</table>

*PR = partial response; NR = no response.
†MSKCC = Memorial Sloan-Kettering Cancer Center (New York, N.Y.); MDACC = M. D. Anderson Cancer Center (Houston, Tex.). The Mayo Clinic is located in Rochester, Minn.
‡Loading dose followed by infusion of 350 mg/m² per day to a target of 280-300 μg/mL.
§Loading dose followed by infusion of 450 or 500 mg/m² per day to a target of 300 μg/mL.
||Intermittent bolus infusions maintaining concentrations in range of 200-300 μg/mL, 175-275 μg/mL, or 150-250 μg/mL until dose-limiting toxic effects observed.
||Adaptive control without computer simulation, maintaining plasma concentrations in the range of 150-250 μg/mL.
** > 80% decline.

baseline, and 17 of 31 (55%; 95% confidence interval = 37%-72%) demonstrated a greater than 75% reduction from baseline. Pain relief was noted in 83% of cases (95% confidence interval = 68%-98%). Why, then, is the drug so controversial?

Is it Effective?

Assessing treatment benefit in prostatic cancer can be difficult, because few cases present with bidimensionally measurable tumor masses. The observed responses in the trial conducted by Eisenberger et al. (14) and in the NCI series (15) are promising but need additional confirmation. Further, even in patients with documented, measurable disease regression, simultaneous progression may be observed in bone. This situation has led to the investigation of alternative clinical trial end points, such as pain relief, or changes in a biochemical parameter, such as PSA (16). These end points must be interpreted cautiously.

The results in terms of palliation of pain are encouraging and suggest a possible role for suramin in patients with painful metastatic lesions. This may be due to the analgesic effects of suramin (17) and/or a direct effect on bone osteoblasts (18). However, while pain relief is an important therapeutic aim, it does not mean that an antitumor effect has been achieved. For example, Tannock et al. (19) noted an improved quality of life, including pain relief, in 30% of patients treated with low-dose prednisone. The contribution of hydrocortisone to the improved pain relief and antitumor effect may be significant. Similarly, we have observed pain palliation in up to 60% of patients treated with bone-seeking radioisotopes, while PSA declines, indicative of antitumor activity, were observed in less than 10% of patients (20). A "placebo" effect is likewise possible.
The Therapeutic Window: Toxic Effects Versus Efficacy

The target concentration of 280-300 µg/mL used by Myers et al. (8) was derived from phase I investigations at the NCI. In these investigations, no responses were observed in patients who had peak plasma suramin concentrations of less than 200 µg/mL. Dose-limiting toxic effects, particularly the frequency of neurotoxicity, became prohibitive above 350 µg/mL (26). A "therapeutic window" of 200-300 µg/mL was therefore postulated, and monitoring of plasma concentration became an integral part of therapy. Further support for the concept was provided by an in vitro study (27) that used primary prostate epithelial cultures. The results suggested that concentrations in the range of 100-160 µg/mL could stimulate growth (27). A inhibitory effect on transforming growth factor-β, known to inhibit prostatic epithelial cell proliferation, was proposed.

The observation that 80% (28 of 35) of patients in the study by Eisenberger et al. (14) discontinued therapy because of dose-limiting toxic effects suggests a limited role for suramin. In particular, four of six patients developed grade IV neurologic dysfunction in the study's cohort I, for which the target suramin plasma concentration was 200-300 µg/mL. The trough level was based on the NCI results described above (15). It must be remembered, however, that this trial was designed to treat patients until dose-limiting toxicity or disease progression was documented. Further, on closer inspection, it is apparent that dose-limiting toxicity did not develop until the 3rd month of continuous treatment and that the frequency and severity of these toxic effects decreased as plasma concentrations were reduced to the range of 150-250 µg/mL. Thus, follow-up, with respect to both toxicity and efficacy, of patients treated in the range of 100-200 µg/mL is awaited. At Memorial Sloan-Kettering Cancer Center, we have not observed severe neuropathies using shorter durations of treatment in the same concentration range (28). Thus, it is likely that both concentration and time factors are important.

Our experience also suggests that "responding" patients can be identified early, a situation that has led to the design of shorter treatment schedules that should be safer with respect to toxic effects. Shorter schedules may also show that long-term hydrocortisone replacement may not be necessary, further reducing toxic effects. Finally, the significance of transient peaks above 350 µg/mL is probably overstated.

Schedule Dependency

Fig. 1 shows three dosing schema. The first is the original slow infusion to a target concentration, the second uses short infusions to maintain concentrations in a defined range [similar to those reported by Eisenberger et al. (14)], and the third loads to the target and maintains concentrations at the target by periodically reducing the rate of the infusion. Biologically, the results are different with respect to toxic effects. For example, the frequency of the vortex keratopathy, coagulopathy, and infection was significantly lower in the Eisenberger et al. trial (14), which used short infusions, compared with treatment by continuous infusion. The importance of schedule on therapeutic effect is unknown. Preliminary data suggest that the efficacy is greatest when schedules with pulsatile flow are used. Considering tumor regression as the outcome measure, a flat infusion schedule seems the least active (29). The role of the tumor vasculature in the delivery of suramin to the central reaches of the tumor is unknown (30,31).

Is Plasma Concentration Monitoring Necessary?

The observation of significant interpatient and intrapatient kinetic variability was based on a small cohort of patients (13). As clinical experience has evolved, it is clear that the overall interpatient and intrapatient kinetic variability is small and that empiric dosing—maintaining suramin concentration in a defined range—can be achieved safely. Thus, intensive pharmacologic monitoring is not necessary. Indeed, trials without adaptive control are currently under way at Memorial Sloan-Kettering Cancer Center, the University of Maryland, the NCI, and the University of Chicago. These trials will allow more widespread use of suramin, and the investigation of combinations with other chemotherapeutic agents (32), biologic agents (33), and radiation therapy (34), with which suramin has shown synergy in vitro.

While questions remain, if the findings from several groups using a variety of schedules are combined, suramin results in measurable disease regression in 27% (35 of 131) of patients and posttherapy declines in PSA in 43% (74 of 173) of patients. While it is likely that hydrocortisone does contribute to the observed response proportion, durable responses such as those reported by Eisenberger et al. (14) and in the NCI trial (25) are unusual with hydrocortisone
alone. A randomized comparison of suramin plus hydrocortisone versus hydrocortisone alone, using a survival end point, would be necessary to evaluate the effect of hydrocortisone. Such a trial was designed and activated but closed for lack of accrual. At Memorial Sloan-Kettering Cancer Center, patient entry in suramin studies is restricted to those patients who have progressed on corticosteroid. Alternatively, a randomized comparison with a pain relief end point can be utilized. Taken together, the results to date clearly justify testing. However, in parallel with the clinical development, laboratory studies must continue to unravel the tumoricidal mechanisms involved so that more specific inhibitors can be developed.

References

(37) Dawson N: Personal communication, 1990

Notes

Affiliations of author: Genitourinary Oncology Service, Division of Solid Tumor Oncology, Memorial Sloan-Kettering Cancer Center, New York, N.Y., and Department of Medicine, Cornell University Medical College, New York, N.Y.

Correspondence to: Howard J, Scher, M.D., Memorial-Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10021.

Supported by Public Health Service grants CA-05826 and CA-09207 and by the Martin Himmel Fund.

Manuscript received March 22, 1993; accepted March 23, 1993.