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. Suramin was evaluated in prostatic cancer on the basis of 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...
A "placebo" effect is likewise possible. 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 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 (23) 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.

These caveats aside, the use of the decline of PSA after therapy as an outcome measure for clinical trial should be considered a part of a sequence of trials. Agents that produce a predefined degree of decline that is maintained on multiple determinations (e.g., 50% or 80% from baseline or normalization) should be tested further. The precise criteria will require prospective validation. Nevertheless, the observation that a posttherapy change in PSA is associated with a survival benefit in the NCI study (75), in the current trial conducted by Eisenberger et al. (14), and in our own experience using other nonhormonal approaches provides further support for this methodology (25). If confirmed, this association should allow the more rapid identification of potentially active compounds.

### 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></td>
<td></td>
<td></td>
<td>No.</td>
<td>PR</td>
</tr>
<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>NR</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>(41)</td>
<td>Intermittent bolus infusions</td>
<td>24</td>
<td>12 (50%)</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></td>
<td></td>
<td>Total</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 400 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. # Loading dose, continuous infusion for 1 week, intermittent bolus administrations to maintain concentrations in range of 150-250 µg/mL. ** >80% decline.
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.
References

(37) Dawson N: Personal communication, 1990

Notes

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