A Phase I Study of SR-2508 and Cyclophosphamide Administered by Intravenous Injection

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ABSTRACT

SR-2508, a less lipophilic and neurotoxic analogue of the nitroimidazole, misonidazole, has exhibited significant chemosensitization properties in preclinical studies with alkylating agents. A phase I trial was carried out to assess toxicity and possible pharmacological interactions of the combination of short infusions of SR-2508 and cyclophosphamide (CP). Patients were randomly assigned to receive either CP alone followed in 3 wk by CP + SR-2508, or CP + SR-2508 followed by CP alone. Additional courses were CP + SR-2508. The maximum tolerated dose of the combination was determined by dose escalation of SR-2508 while the dose of CP remained fixed, initially 1.0 g/m², and a second maximum tolerated dose was determined with CP at 1.6 g/m². One hundred seventeen evaluable courses were administered to 39 patients, the majority of whom had received prior treatment. Somewhat unexpectedly, reversible grade 4 granulocytopenia was the dose-limiting toxicity occurring in four of five evaluable first combination courses at level 6 (SR-2508, 11.3 g/m²; CP, 1.0 g/m²), the initial maximum tolerated dose. SR-2508 enhanced CP-induced myelosuppression as exhibited by the significant difference (p < 0.001) between the 27 paired courses (CP versus CP + SR-2508) for WBC nadirs over levels 1 to 6. The neurotoxicity encountered was similar to that seen in past clinical trials, being reversible, mild, and usually peripheral in nature. There was one treatment-related death (neutropenic sepsis) on study. No other significant toxicity was seen. SR-2508 exhibited linear pharmacokinetics over the dose range studied. The SR-2508 area under the concentration-time curve increased linearly with dose (r = 0.858; p < 0.001). No other parameters were dose related. Neither drug appeared to affect the pharmacokinetics of the other, and CP pharmacokinetic values were consistent with those from prior studies. Due to the interaction noted between the two agents and the preclinical data suggesting preferential enhancement of antitumor efficacy under this combination, phase II study appears warranted.

INTRODUCTION

Extensive preclinical data suggest that nitroheterocyclic compounds, such as MISO,7 can selectively potentiate the antitumor activity of certain bifunctional alkylating agents, most notably L-PAM and CP and several of the nitrosoureas (1–3), a phenomenon referred to as chemosensitization or chemopotentiation. The exact mechanism(s) of the chemopotentiation induced by nitroheterocyclic compounds is uncertain, but possible mechanisms include manipulation of the glutathione oxidation reduction system, alteration of the antitumor agent's pharmacokinetics, or enhanced DNA-DNA cross-link formation (3). Numerous laboratories have reported that the combination of MISO and chemotherapy for the treatment of murine tumors typically results in dose enhancement factors of up to 2.0 for tumor response without significant increases in concomitant normal tissue toxicity (3). This consistent, preferential enhancement of tumor response led to limited evaluation of this treatment strategy in the clinic.

However, in contrast to animal experiments, early clinical trials of chemosensitization failed to establish any significant antitumor benefit for combination chemotherapy including MISO. A careful review of the clinical and preclinical data suggests that many of these trials were not optimally designed to examine the effectiveness of the sensitizer drug strategy and, in fact, examined sites or drug combinations contraindicated by analysis of currently available experimental data (4). Nevertheless, these initial trials clearly demonstrated that MISO could be administered in combination with several chemotherapeutic agents including L-PAM (5, 6), CP (7, 8), BCNU (9), and CCNU (10, 11) without significant enhancement of normal tissue toxicity.

A notable exception to the otherwise negative clinical experience with chemosensitization was recently reported by Coleman et al. (6). In a prospective randomized phase II trial, these investigators demonstrated that the response rate in patients with non-small cell lung cancer treated with a combination of MISO and L-PAM was significantly better than that of patients treated with L-PAM alone. This provocative observation, combined with the realization of possible problems with earlier trials, has prompted renewed interest in the strategy of combining sensitizing agents with systemic chemotherapy for the treatment of human cancers.

Toxicity studies revealed that the dose of MISO which can be safely administered to patients receiving systemic chemotherapy is frequently limited to approximately 12 g/m² by neurotoxicity manifested as peripheral neuropathies (12, 13). This limitation has prompted the search for less toxic compounds offering similar or improved chemosensitizing properties. While no other potential chemosensitizing agent approved for clinical use in the United States has been found to be a more effective chemosensitizing agent than MISO in experimental systems, there is considerable interest in evaluating the clinical potential of SR-2508 (Etanidazole), a hydrophilic analogue of MISO. This compound has been shown to be comparable to MISO in its ability to preferentially enhance the antitumor activity of CP in some experimental systems (14), yet approximately 3 times the concentration of SR-2508 can be administered before encountering comparable dose-limiting neurotoxicity (15, 16). The ability to deliver more SR-2508 could conceivably translate to significantly larger enhancements.
than are possible with MISO, as preclinical studies indicate that the sensitizing effects of nitroimidazoles are generally proportional to dose. On the basis of its favorable clinical characteristics and demonstrated ability to selectively enhance developed grade 4 granulocytopenia, or >grade 3 thrombocytopenia or 6 patients who upon receiving their first course of CP + SR-2508 during a course of CP + SR-2508, the dose of CP was reduced by 50% scheduled antiemetics, including pretreatment. All patients were ran this bifunctional alkylator.

**MATERIALS AND METHODS**

**Patient Selection.** Individuals with advanced cancer for whom no standard effective therapy was available, who gave informed consent according to institutional and Food and Drug Administration guidelines, and who had adequate bone marrow (WBC, ≥4,000/mm³; platelet count, ≥100,000/mm³), renal (serum creatinine, ≤1.6 mg/dl in women and ≤1.8 mg/dl in men; or creatinine clearance, ≥60 mL/min), hepatic (aspartate aminotransferase, ≤5 x normal; and bilirubin, ≤1.5 mg/dl), and metabolic (calcium, <11.0 mg/dl) functions were eligible. Patients who had an ECOG performance status >2, a symptomatic peripheral neuropathy, a life expectancy of <12 wk, and who had received radiation therapy within 2 wk or chemotherapy or biological therapy within 4 wk were not eligible.

**Drug Formulation.** SR-2508 was supplied by the National Cancer Institute in 1-g vials which were reconstituted with 19.4 mL of NS without preservative to a concentration of 50 mg/mL. SR-2508 was administrated as a short i.v. infusion (total volume, 250 to 550 mL of NS) at a concentration of ≤50 mg/mL. CP was prepared in the standard fashion and administered in a short infusion through a peripheral or central site.

**Drug Administration and Dose Escalation.** The drugs were administered concomitantly with 1 liter of NS over a 2-h and 20-min time period. CP was administered i.v. over the first 20 min at doses of 1.0 g/m² or 1.6 g/m², and SR-2508 was given i.v. over 20 min starting 2 h after the start of the CP infusion. Patients initially received either prochlorperazine (10 mg) or haloperidol (1 mg) and lorazepam (1 mg) on an as-needed basis only; with later courses the patients received scheduled antiemetics, including pretreatment. All patients were randomized to receive either CP alone as their first course and CP + SR-2508 as the second course, or CP + SR-2508 followed by CP alone. Subsequent courses were with CP + SR-2508.

The SR-2508 escalation scheme was as follows: level 1, 3 g/m²; level 2, 4 g/m²; level 3, 5 g/m²; level 4, 6.7 g/m²; level 5, 8.7 g/m²; and level 6, 11.3 g/m². A minimum of three patients was treated and evaluated for ≥3 wk at each dose level. If ≥grade 3 myelosuppression or ≥grade 3 vomiting occurred in ≤2 patients and no cardiac, hepatic, or renal toxicity occurred, then the next three patients were entered at the next higher SR-2508 dose level. An individual patient’s SR-2508 dose was neither escalated nor reduced while on study.

If grade 4 granulocytopenia or grade 3 thrombocytopenia occurred during a course of CP + SR-2508, the dose of CP was reduced by 50% for subsequent combination courses.

The MTD of SR-2508 was defined as that dose level at which ≥3 of six patients who upon receiving their first course of CP + SR-2508 developed grade 4 granulocytopenia, or ≥grade 3 thrombocytopenia or ≥grade 3 vomiting despite aggressive antiemetic use, or ≥grade 2 neurotoxicity or other nonhematological toxicity. The MTD for SR-2508 was initially determined at a CP dose of 1.0 g/m², and then a second MTD was determined for a CP dose of 1.6 g/m² starting three levels below the initial MTD level. The ECOG toxicity criteria were used to grade all toxicity during the trial.

Hematological and nonhematological parameters were monitored weekly.

**Pharmacokinetic Methods.** Heparinized blood samples were collected pretreatment (assay blank) and at the following times postinfusion: 0 (exact end of infusion), 15, 30, 45, 60, and 90 min; and 2, 4, 6, 8, 12, and 24 h. Additional samples were obtained to yield a similar postinfusion sampling schedule for SR-2508. Sampling times were altered slightly as circumstances dictated. Plasma was immediately separated and stored at −80°C until analysis. Urine was collected from the start of the CP infusion during the following intervals: 0 to 4, 4 to 8, 8 to 12, and 12 to 26 h (10 to 24 h after the SR-2508 infusion). Total urine volumes were measured, and aliquots were frozen at −80°C until assay.

**RESULTS**

A total of 119 evaluable courses (2 additional courses were unevaluable) were given to 39 patients, the majority of whom had received prior treatment (see Table 1). Adenocarcinoma of the gastrointestinal system and kidney along with non-small cell lung cancer comprised the majority of the patients (29 of 39).

**SR-2508 Pharmacokinetics.** Twenty-nine courses of SR-2508 with 1.0 g/m² of CP were available for complete pharmacokinetic evaluation; the SR-2508 pharmacokinetic parameters are

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female ratio</td>
</tr>
<tr>
<td>Median age (yr)</td>
</tr>
<tr>
<td>Performance status (no.)</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>Primary diagnosis (no.)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Renal</td>
</tr>
<tr>
<td>Lung</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>Prior therapy (no.)</td>
</tr>
<tr>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Radiotherapy</td>
</tr>
<tr>
<td>Both</td>
</tr>
<tr>
<td>None</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, range.
were dose related. In seven patients, SR-2508 pharmacokinetics was not apparently altered in these repeat courses when compared with the first course in the same patient. Mean values for $C_{L0}$ for the first and repeat courses were 3.3 liters/h/m² and 3.0 liters/h/m² ($P = 0.09$); the harmonic mean terminal half-life ($t_{\beta}$) was identical for each group, 5.5 h. SR-2508 pharmacokinetics was also measured in four patients receiving 5 g/m² of SR-2508 with the 1.6-g/m² dose of CP. No difference in any SR-2508 pharmacokinetic parameter was observed in this group when compared with the group of patients who received the same dose of SR-2508 with 1.0 g/m² of CP.

Cyclophosphamide Pharmacokinetics. The possible effect of SR-2508 on CP pharmacokinetic parameters was evaluated in patients who received paired courses of CP alone and CP with SR-2508. Twenty-three patients had paired courses at a CP dose of 1.0 g/m², and four additional patients had paired courses at 1.6 g/m² of CP. The pharmacokinetic data for CP are summarized in Table 3. No significant difference in any CP pharmacokinetic parameter was seen in courses of CP alone versus course of the combination in the same patient as analyzed by the paired $t$ test. No differences in CP metabolism measured as total alkylating activity expressed as NNME were observed. Of note, intact CP exhibited linear pharmacokinetics: the $C_{L0}$ of intact CP at 1.6 g/m² was not significantly different from that at 1.0 g/m²; however, there were significant alterations in the alkylating activity parameters: AUC and peak concentrations exhibited a 2.5-fold increase, although the dose was only increased by 60%, and the time of peak alkylating activity increased from 2.4 to 3.5 h.

The SR-2508 and CP pharmacokinetic parameters reported here are similar to those from previous studies for short infusions of these drugs (16, 18, 20). No pharmacokinetic interactions were observed.

Toxicity. Bone marrow suppression, specifically granulocytopenia (<500 cells/mm³) was the dose-limiting toxicity of the combination. Reversible Grade 4 granulocytopenia occurred in four of five evaluable first courses with CP (1.0 g/m²) and SR-2508 (11.3 g/m²) and only in one of six patients at the SR-2508 level (8.7 g/m²) preceding the MTD level (see Table 4). SR-2508 showed enhancement of CP-induced myelosuppression as evidenced by the significant difference ($P < 0.001$) in WBC count nadirs between the 27 randomly ordered paired courses, CP versus CP + SR-2508 (Fig. 1). Examining each dose level separately revealed that this difference was significant at levels 2, 3, 5, and 6 (4.0, 5.0, 8.7, and 11.3 g/m² of SR-2508, respectively, with 1.0 g/m² of CP, $P < 0.05$ in each case by paired $t$ test). An example of the difference in myelosuppression between courses with and without SR-2508 at an individual dose level is shown for the MTD level (11.3 g/m²), where the mean WBC nadir of CP alone was 3800/mm³ compared with 1400/mm³ for CP + SR-2508 ($P = 0.01, n = 6$).

Significant bone marrow suppression occurred at the first SR-2508 level (5.0 g/m²) in patients receiving 1.6 g/m² of CP (see Table 4). As expected, it was more difficult to show enhancement of bone marrow toxicity by SR-2508 at the higher CP dose with no significant difference in WBC count nadirs between paired courses being seen. No patients exhibited >grade 1 thrombocytopenia during this study.

Cumulative marrow toxicity for repeated courses of CP + SR-2508 was minimal and similar to the expected cumulative toxicity of CP. Levels 1 to 5 had only two patients (level 3, course 5, and level 3, course 4) with a first episode of grade 4 granulocytopenia occurring after course 2. Patients at level 6 (11.3 g/m²) and patients given the higher CP dose plus SR-2508 (5.0 g/m²) who developed grade 4 granulocytopenia on the combination course had their CP dose decreased by 50%, to 500 mg/m² and 800 mg/m², respectively. Subsequent courses with the dose reduction in CP but 100% SR-2508 dose were not accompanied by any significant granulocytopenia (>grade 2), thus reinforcing the view that SR-2508 was not directly marrow suppressive in these patients.

A neurologist examined each patient prior to every course of therapy, and only patients at levels 1 to 5 had the Purdue pegboard test (23) done prior to each course, which showed no change in results within patients from course to course. The early patients also underwent NCV and somatosensory evoked response studies prior to treatment. A majority of the patients refused the post-study examinations. The neurological toxicity seen was reversible, mild, and similar to toxicity encountered in prior work with MISO and SR-2508 (16, 24). Seven of 39 patients developed either symptoms or signs of a peripheral neuropathy. One of these seven patients and one additional patient possibly had neurological toxicity, syncope and ototoxicity, which has been reported with MISO and SR-2508 (16, 24). One patient had two syncopal episodes on day 2 of course 2, level 3 (first dose of SR-2508 at 5.0 g/m²), which were preceded by nausea and presumed to be of vasovagal origin. In that patient, a computerized tomography scan of the brain was normal, the electroencephalogram showed focal slowing, and the serum sodium was 121 meq/liter. The patient had no further syncopal episodes and received no further courses on study. A repeat electroencephalogram obtained 3 wk later was unchanged.

Peripheral neuropathy (the usual neurological toxicity seen with nitroimidazoles) seen during this trial was reversible, pre-

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**Table 2 SR-2508 pharmacokinetic parameters (first combination courses with 1.0 g/m² of CP)**

<table>
<thead>
<tr>
<th>Dose of SR-2508 (g/m²)</th>
<th>No. of patients</th>
<th>Peak $C_p$^a (nm)</th>
<th>AUC (h × mm)</th>
<th>$C_L0$ (liter/h/m²)</th>
<th>$V_w$ (liter/m²)</th>
<th>$t_{1/2}$ (h)</th>
<th>Urine recovery (% of dose/24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0</td>
<td>3</td>
<td>1.10 ± 0.40</td>
<td>4.90 ± 1.5</td>
<td>3.0 ± 1.0</td>
<td>28.9 ± 4.3</td>
<td>7.1^</td>
<td>78.0 ± 15.0</td>
</tr>
<tr>
<td>4.0</td>
<td>3</td>
<td>2.04 ± 0.82</td>
<td>4.91 ± 1.3</td>
<td>4.0 ± 1.0</td>
<td>18.5 ± 1.9</td>
<td>4.4</td>
<td>92.9 ± 5.5</td>
</tr>
<tr>
<td>5.0</td>
<td>8</td>
<td>2.10 ± 0.41</td>
<td>7.90 ± 2.1</td>
<td>3.1 ± 0.7</td>
<td>22.6 ± 2.1</td>
<td>5.7</td>
<td>78.4 ± 7.4</td>
</tr>
<tr>
<td>6.7</td>
<td>4</td>
<td>2.79 ± 0.64</td>
<td>9.62 ± 1.7</td>
<td>3.3 ± 0.6</td>
<td>23.4 ± 3.5</td>
<td>5.4</td>
<td>82.4 ± 11.9</td>
</tr>
<tr>
<td>8.7</td>
<td>5</td>
<td>3.46 ± 0.83</td>
<td>11.1 ± 3.2</td>
<td>3.9 ± 1.2</td>
<td>23.7 ± 2.3</td>
<td>4.8</td>
<td>74.6 ± 22.0</td>
</tr>
<tr>
<td>11.3</td>
<td>6</td>
<td>4.75 ± 1.14</td>
<td>18.6 ± 5.0</td>
<td>3.0 ± 0.7</td>
<td>20.3 ± 3.5</td>
<td>5.3</td>
<td>76.8 ± 3.8</td>
</tr>
</tbody>
</table>

Overall mean 29 3.3 ± 0.9 22.6 ± 3.8 5.3 79.6 ± 12.6

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^a $C_p$: plasma concentration; $V_w$: steady-state volume of distribution; $t_{1/2}$, terminal phase half-life.

^b Mean ± SD.

^c Harmonic mean.

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Table 3 Cyclophosphamide pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Dose of CP (g/m²)</th>
<th>AUC (h × mM)</th>
<th>( C_{Lm} ) (liter/h/m²)</th>
<th>( V_{ss} ) (liter/m²)</th>
<th>( t_{1/2} ) (h)</th>
<th>Urine recovery (% of dose/24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP alone</td>
<td>1.57 ± 0.29 *</td>
<td>2.54 ± 0.53</td>
<td>22.9 ± 3.4</td>
<td>6.20</td>
<td>13.9 ± 6.2</td>
</tr>
<tr>
<td>CP + SR-2508</td>
<td>1.56 ± 0.38</td>
<td>2.63 ± 0.77</td>
<td>22.1 ± 3.1</td>
<td>5.80</td>
<td>13.7 ± 5.7</td>
</tr>
<tr>
<td>( P ) value (n = 23)</td>
<td>0.87</td>
<td>0.48</td>
<td>0.20</td>
<td>0.10</td>
<td>0.80</td>
</tr>
<tr>
<td>1.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP alone</td>
<td>2.40 ± 0.20</td>
<td>2.57 ± 0.22</td>
<td>20.7 ± 0.22</td>
<td>5.50</td>
<td>12.1 ± 2.8</td>
</tr>
<tr>
<td>CP + SR-2508</td>
<td>2.32 ± 0.18</td>
<td>2.69 ± 0.21</td>
<td>21.6 ± 3.2</td>
<td>5.60</td>
<td>8.6 ± 2.8</td>
</tr>
<tr>
<td>( P ) value (n = 4)</td>
<td>0.42</td>
<td>0.34</td>
<td>0.13</td>
<td>0.67</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Total alkylation activity (NNME)

<table>
<thead>
<tr>
<th>Dose of CP (g/m²)</th>
<th>AUC (0–24 h) (h × μM)</th>
<th>Time to peak ( C_{p} ) (h)</th>
<th>Peak ( C_{p} ) (μM)</th>
<th>Urine excretion (as % of CP dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP alone</td>
<td>278 ± 96</td>
<td>2.4 ± 0.8</td>
<td>14.6 ± 4.3</td>
<td>20.0 ± 6.2</td>
</tr>
<tr>
<td>CP + SR-2508</td>
<td>274 ± 62</td>
<td>2.5 ± 0.9</td>
<td>15.4 ± 4.0</td>
<td>17.1 ± 5.3</td>
</tr>
<tr>
<td>( P ) value (n = 23)</td>
<td>0.78</td>
<td>0.62</td>
<td>0.35</td>
<td>0.053</td>
</tr>
<tr>
<td>1.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP alone</td>
<td>711 ± 117</td>
<td>3.4 ± 0.1</td>
<td>38.2 ± 8.4</td>
<td>17.8 ± 3.4</td>
</tr>
<tr>
<td>CP + SR-2508</td>
<td>632 ± 82</td>
<td>3.6 ± 1.4</td>
<td>37.1 ± 5.4</td>
<td>19.0 ± 3.3</td>
</tr>
<tr>
<td>( P ) value (n = 4)</td>
<td>0.16</td>
<td>0.75</td>
<td>0.62</td>
<td>0.81</td>
</tr>
</tbody>
</table>

\* \( V_{ss} \), steady-state volume of distribution; \( t_{1/2} \), terminal phase half-life; \( C_{p} \), plasma concentration.
\* Mean ± SD.
\* Harmonic mean.
\* \( P \) value from paired \( t \) test.

Table 4 Toxicity of evaluable first courses of CP + SR-2508 and CP alone

<table>
<thead>
<tr>
<th>Level</th>
<th>Dose of SR-2508 (g/m²)</th>
<th>&lt;Grade 3</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>&lt;Grade 2</th>
<th>Grade 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 g/m² of CP</td>
<td></td>
<td>3/3 (2/3) *</td>
<td>0/3 (0/2)</td>
<td>0/3 (0/2)</td>
<td>0/3 (1/2)</td>
<td>3/3 (1/2)</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>3/3 (3/3)</td>
<td>0/3 (0/3)</td>
<td>0/3 (0/3)</td>
<td>0/3 (1/3)</td>
<td>3/3 (2/3)</td>
</tr>
<tr>
<td>3</td>
<td>4.0</td>
<td>9/9 (10/10)</td>
<td>0/9 (0/10)</td>
<td>0/9 (0/10)</td>
<td>3/9 (6/10)</td>
<td>6/9 (4/10)</td>
</tr>
<tr>
<td>4</td>
<td>5.0</td>
<td>6/4 (3/3)</td>
<td>0/4 (0/3)</td>
<td>0/4 (0/3)</td>
<td>2/4 (2/3)</td>
<td>2/4 (1/3)</td>
</tr>
<tr>
<td>5</td>
<td>6.7</td>
<td>2.6 (4/4)</td>
<td>2/6 (0/4)</td>
<td>2/6 (0/4)</td>
<td>2/6 (2/4)</td>
<td>2/6 (2/4)</td>
</tr>
<tr>
<td>6</td>
<td>8.7</td>
<td>1.5 (6/6)</td>
<td>1/5 (0/6)</td>
<td>4/5 (0/6)</td>
<td>0/5 (2/6)</td>
<td>5/5 (4/6)</td>
</tr>
<tr>
<td>1.6 g/m² of CP</td>
<td></td>
<td>5.0</td>
<td>0/6 (2/6)</td>
<td>1/6 (1/6)</td>
<td>5/6 (3/6)</td>
<td>3/6 (4/6)</td>
</tr>
</tbody>
</table>

\* Numbers in parentheses, CP-alone courses.
\* One patient with Grade 3 nausea and vomiting.
\* Prechemotherapy antiemetics given.

Fig. 1. WBC nadir for paired courses in 33 patients over the course of this trial as described in the text.

The remaining five patients had cumulative SR-2508 doses ranging from 25 g/m² over 18 wk to 50 g/m² over 33 wk. They had symptoms or signs of a mild peripheral neuropathy which was reversible over a few weeks. The only abnormal posttreatment NCV was found in an asymptomatic patient who had received 35 g/m² over 24 wk and had a questionable abnormal neurological examination at course 5 which did not change with three additional courses. Follow-up electrophysiologic studies found the patient to have moderate-to-severe axonal sensory > motor peripheral neuropathy. Overall, five of 10 patients who received cumulative doses of >20 g/m² developed grade 1 or 2 neurotoxicity as described. Numerous patients had previously received neurotoxic drugs, i.e., Vinca alkaloids and cisplatin, or had evidence by neurological examination of a preceding asymptomatic peripheral neuropathy due to diabetes or cancer and did not develop any neurotoxicity.

There were two deaths on study during the trial. The first...
due to progressive liver deterioration. Evaluation pre- and post-
patient died at a local hospital on day 13 of course 4 (CP, 1.0
g/m²; SR-2508, 5.0 g/m²) due to neutropenic sepsis (no autopsy
due to progressive liver deterioration. Evaluation pre- and post-
and SR-2508 in combination with CP or other bifunctional alkylating agents revealed little if any effect of the sensitizer on
myelosuppression (14).

Previous clinical studies with CP and MISO were not predictive
of the enhanced toxicity observed in our trial. Two phase I
trials examining the MISO/CP combination both concluded
that the addition of MISO to systemic therapy with CP did not
significantly potentiate myelotoxicity (7, 26). Three additional
studies, two examining combinations of MISO with CCNU
(10, 11) and the third examining a MISO/L-PAM combination
(5), all support a similar conclusion. The apparent discrepancy
between these previous clinical trials and our SR-2508 experi-
ence may be related to differences between the two sensitzers
themselves, differences in trial design, treatment schedule, route
of administration, or total sensitizer doses examined. While the
two sensitzers do display certain distinct properties, it is cur-
dently difficult to attribute the apparent differential enhance-
ment of CP myelotoxicity to any of these. It likewise seems
unlikely that treatment schedule can fully account for the dif-
fences, as similar schedules were utilized in all the studies.
Certainly, differences in sensitizer doses could conceivably be
contributing factors as much larger single doses of SR-2508
were examined in the current studies.

However, it seems more likely that failure to detect potentia-
ment of myelotoxicity in previous MISO trials may at least
partially be attributable to the fact that the MISO trials were
not designed to permit comparison of toxicity of CP adminis-
tered alone and in combination with sensitizer in paired courses
in individual patients, as was done in our current study. In
support of this possibility is clinical evidence implicating MISO
in the enhancement of chemotherapy-related hematological
toxicity at MISO doses comparable to those examined in the
studies described above. In an ECOG-sponsored phase II trial
of MISO and CP in metastatic renal carcinoma, 67% of the
patients experienced severe (42%) or life-threatening (25%)
hematological toxicity (8). Although not designed as a toxicity
study, these data prompted the authors to suggest that con-
trolled studies should be considered in order to determine
whether MISO augments the hematological toxicity of CP.
Similarly, Brower et al. (27) observed severe myelosuppression
in small cell lung cancer patients treated with MISO in com-
bination with CP, CCNU, and methotrexate. The frequency of
hematological toxicity greatly exceeded that encountered in a
previous ECOG trial of the methotrexate combination, prompt-
ing early termination of the study. Collectively, the clinical
experience suggests that the combination of nitroimidazole
chemosensitizers with bifunctional alkylators may not be as
benign as suggested by murine studies. This possibility should
be considered in the design of future clinical trials.

Sensitizer-induced alteration of drug pharmacokinetics has
been suggested to be at least partially responsible for chemo-
sensitization following administration of large doses of MISO
in combination with certain nitrosoureas, L-PAM and CP (2,
3). However, enhancements of antitumor effectiveness have also
been observed without alterations in the pharmacology of the
cytotoxic agent. In contrast to MISO, SR-2508 does not pro-
duce alterations in the pharmacokinetic properties of these
drugs in rodent tumor models, even when administered in large
doses (28–30). To date, no significant alterations have been
detected in clinical trials combining MISO with cytotoxic drugs
(7, 26), although Coleman et al. found that plasma L-PAM
concentrations were approximately 25% higher in MISO-treated patients. As shown in Table 2, SR-2508 did not alter the pharmacokinetic properties of CP, assayed either as parent compound or total alkylating equivalents. Analyses of SR-2508 pharmacokinetic parameters were consistent with those observed previously in radiation sensitization trials (15, 16). This, in conjunction with our data showing no difference in SR-2508 pharmacokinetics between Levels 3 and 7, indicates that there was no effect of CP administration on SR-2508.

Radiation sensitizer clinical studies have already identified neurotoxicity, manifested primarily as paresthesias, as being dose limiting for both MISO and SR-2508 (12, 13, 15, 16). Consequently, our initial expectation was that the dose of SR-2508 that could be administered with chemotherapeutic drugs would also be limited by peripheral neuropathies. However, since in the chemosensitization setting SR-2508 was to be administered over a longer period of time and with a longer interval between consecutive doses than is common when the agent is used as a radiation sensitizer, it was conceivable that larger cumulative doses might be tolerated. One objective of our study was to evaluate this possibility. In general, neurotoxicity was not a problem in this trial, and the types of abnormalities noted were comparable in description and magnitude to those encountered in the radiation trials. Mild, reversible neuropathies were observed at cumulative SR-2508 doses ranging from 20 to 50 g/m². Unfortunately, we were not able to adequately evaluate the relationship between neurotoxicity and total SR-2508 dose in this chemosensitization protocol owing to difficulties in administering enough courses to individual patients receiving low SR-2508 doses and the myelotoxicity encountered at the higher doses. On the basis of our limited experience, however, it seems most prudent to assume that the dose-response relationship for neurotoxicity is comparable whether SR-2508 is used as a radiation sensitizer or as a chemosensitizer. The enhancement of hematological toxicity attributable to the addition of SR-2508 to chemotherapy with CP, while unexpected, is nevertheless encouraging, as it suggests that there is an interaction between these two agents. Further clinical studies of this treatment combination appear warranted, especially in light of extensive preclinical data suggesting preferential enhancement of antitumor efficacy in animal tumor models by such combinations (1–3). Considerations for additional phase I testing of the combination consist of examining infusion delivery or administering SR-2508 prior to the alkylator, since the optimum delivery or schedule of nitroimidazoles and alkylators is uncertain and the potential for different dose-limiting toxicity exists. On the basis of our study, we would suggest that an intermediate dose of 1.2 g/m² in combination with 8.7 g/m² of SR-2508 as a short infusion would be appropriate for phase II trials.

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A Phase I Study of SR-2508 and Cyclophosphamide Administered by Intravenous Injection

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