Phase I and Pharmacokinetic Study of Hepsulfam (NSC 329680)


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ABSTRACT

Hepsulfam (NSC 329680), a bifunctional alkylating agent structurally related to busulfan, has entered clinical trial based on its broader preclinical antitumor activity compared with that of busulfan and its i.v. formulation which may circumvent the many problems arising from the p.o. administration of busulfan, such as significant individual differences in bioavailability. In this Phase I study, 53 patients received 95 courses of hepsulfam at doses ranging from 30 to 480 mg/m² administered i.v. over 30 min every 28 days. Hematological toxicity was dose limiting. Leukopenia and thrombocytopenia were dose related, delayed in onset, and sustained for long durations. Toxicity was cumulative in most patients receiving more than one course. This pattern of myelosuppression suggests that hepsulfam is cytotoxic to hematopoietic stem cells. Although hematological toxicity was not particularly severe during most courses, its lengthy duration precluded the prompt administration of subsequent courses. Minimal nonhematological effects were observed. Pharmacokinetic studies revealed that the clearance rate of hepsulfam is linear over the dose range studied and that its plasma disposition is biphasic with mean α and β half-lives of 19 ± 18 (SE) min and 337 ± 248 (SE) min, respectively. The area under the plasma clearance curve correlated with the percentage of change in WBC using a sigmoidal Emax model and with the duration of thrombocytopenia in patients with hematological toxicity. Based on the protracted duration of the toxicity of multiple doses that were >210 mg/m², the recommended starting dose for Phase II trials is 210 mg/m². However, these trials should be pursued with caution because of the protracted nature of hepsulfam's myelosuppression. Because hepsulfam produced minimal nonhematological toxicity, substantial dose escalation above 480 mg/m² may be possible with hematopoietic stem cell support.

INTRODUCTION

Hepsulfam (NSC 329680) is one of a series of bis-sulfamic acid esters that was synthesized in an attempt to improve the antitumor efficacy of busulfan. Both agents possess antineoplastic activity by virtue of their alkylating properties (1). However, the agents differ in both the length of the carbon chains and the polar leaving groups (Fig. 1). The antitumor activity of hepsulfam was initially identified in the i.p. implanted P388 leukemia prescreen (1). In preclinical studies, hepsulfam was demonstrated to be active against both human MX-1 mammary tumor xenografts and murine BALB/c × DBA/8 F1 (hereafter called CD8F) mammary tumors as well as murine B16 melanoma, L1210 leukemia, and colon adenocarcinoma 38, while busulfan was active only against the murine CD8F, mammary carcinoma in the same preclinical screen. Hepsulfam was also found to be significantly more active than busulfan in a combined in vitro and in vivo screening system consisting of human large cell lung cancer and melanoma xenografts (2). In addition, hepsulfam was demonstrated to be superior to busulfan in inhibiting colony-forming units, granulocyte and macrophage, in freshly isolated peripheral mononuclear bone blood cells from patients with chronic myelogenous leukemia (3). The difference in the length of the carbon chain between the electrophilic centers may be an important determinant of the ability of hepsulfam to form DNA interstrand or intrastrand cross-links (4). In fact, hepsulfam was found to produce significant DNA interstrand cross-linking in murine L1210 leukemia cells after drug treatment for 2 h, while busulfan did not (5). Hepsulfam was found to be 2- to 3-fold more cytotoxic than busulfan in two human leukemia (HL-60, K562) and human colon carcinoma (BE, HT-29) cell lines after treatment for 2 to 12 h. In addition, hepsulfam produced DNA interstrand cross-linking in all four cell lines, whereas busulfan did not (6).

In preclinical toxicology studies on BALB/c × DBA/2 F1 (hereafter called CD2F1) mice, the MELD10 was 416.4 mg/m² (1). Hematological toxicity was dose limiting in CD2F1 mice, Fischer 344 rats, and beagle dogs. In beagle dogs, at the MELD10, significant hematological toxicity and gastrointestinal hemorrhage were observed in a single animal. In all cases, toxicity was delayed in onset, cumulative, dose related, and slowly reversible. Ataxia, convulsions, lethargy, and tremors were noted in Fischer 344 rats treated at the highest dose level tested (1.5 MELD10) and in the vehicle-treated control animals.

Busulfan is currently used in high-dose chemotherapy regimens with bone marrow reinfusion and is available only as a p.o. preparation. Its bioavailability is extremely variable in both adult and pediatric patients undergoing bone marrow transplantation which may portend variability in toxicities, such as venoocclusive disease of the liver as well as clinical efficacy (7, 8). The availability of hepsulfam as an i.v. formulation will likely be associated with more predictable disposition compared with busulfan. On the basis of both the broader spectrum of activity in solid tumors compared with that of busulfan and an i.v. formulation, hepsulfam was selected for clinical development.

The purposes of this Phase I trial were (a) to determine the maximally tolerated dose of hepsulfam administered as a short i.v. infusion every 28 days; (b) to describe and quantitate the toxicities of hepsulfam given on this schedule of drug administration; (c) to study the clinical pharmacology of hepsulfam given as a short i.v. infusion and to attempt to correlate this with the major clinical effects; and (d) to seek preliminary evidence of therapeutic activity of hepsulfam in patients with advanced solid tumors.

MATERIALS AND METHODS

Patient Population. Patients with histologically confirmed solid tumors refractory to conventional therapy or for which no effective therapy was known were candidates for entry into this study. Eligibility criteria included: (a) age greater than 18 yr; (b) Eastern Cooperative Oncology Group performance status of 2 or better (ambulatory and able to perform self care); (c) life expectancy of at least 4 wk; (d) no major surgery within 14 days and no large-field radiotherapy within 28 days (6 wk for those treated with mitomycin C or a nitrosourea); (e) adequate bone marrow (WBC ≥ 4,000/μl and platelets ≥ 100,000/μl).

The abbreviations used are: MELD10, single dose lethal to 10% of mice; AUC, area under the plasma clearance curve; AUC6h, AUC that produces 50% of the maximum effect.


\[
\text{NH}_2 - \text{SO}_2 - 0 - (\text{CH}_3)_2 - \text{O} - \text{SO}_2 - \text{NH}_2
\]

**HEPSULFAM**

\[
\text{CH}_4 - \text{SO}_2 - 0 - (\text{CH}_3)_2 - 0 - \text{SO}_2 - \text{CH}_3
\]

**BUSULFAN**

Fig. 1. Chemical structures of hepsulfam and busulfan.

hepatic (total bilirubin \( \leq 1.5 \) mg/dL), and renal (creatinine \( \leq 1.5 \) mg/dL) function; and (f) no other coexistent medical problems of sufficient severity to prevent full compliance with the study. Before entry, all patients had a complete medical history and physical examination performed. The majority of patients had an Eastern Cooperative Oncology Group performance status of either 0 or 1. Height, weight, performance status, and tumor measurements were recorded. Initial laboratory data obtained included a complete blood count, differential, platelet count, serum electrolytes, blood urea nitrogen, creatinine, glucose, total protein, albumin, calcium, phosphate, uric acid, alkaline phosphatase, total and direct bilirubin, serum alanine aminotransferase, serum serine aminotransferase, and prothrombin time. Chest radiograph, urinalysis, electrocardiogram, and baseline pulmonary function tests were also performed. All patients gave written informed consent according to federal and institutional guidelines.

**Dosage and Formulation.** Hepsulfam was supplied by the Division of Cancer Treatment, National Cancer Institute (Bethesda, MD). The drug was provided in a 5-ml flint vial with 150 mg of hepsulfam freeze-dried from 3-butyl alcohol which was then dissolved in 4.8 ml of a mixture composed of 10% ethanol, 40% propylene glycol, and 0.05 M phosphate buffer (pH 7.4) yielding a 30-mg/ml solution. Hepsulfam was diluted in at least 150 ml of 5% dextrose in water or normal saline and infused over 30 min. The starting dose was 30 mg/m\(^2\) administered as a single 30-min infusion every 28 days (approximately 0.1 MELD\(_O\)). This period of infusion was chosen to minimize acute neurological toxicities from the organic phase of the formulated product or the drug itself that had been seen during bolus administration in preclinical studies (1). Patients received their first dose of hepsulfam as an inpatient, and subsequent courses were administered in the outpatient department. The dose was escalated in successive cohorts of new patients according to a modified Fibonacci search scheme to 60, 100, 150, 210, 270, 360, and 480 mg/m\(^2\). A minimum of three patients was entered at each dose level. Dose escalation was initially permitted in patients who did not have toxicity during their previous course and after at least one previously untreated patient had completed a higher dose level. When cumulative toxicity was suspected, dose escalation in a single patient was not permitted. No patient had dose escalation at dose levels above 210 mg/m\(^2\).

Follow-up. Patients were seen weekly while on study, and interim history and physical and laboratory findings were recorded. Toxicity was graded weekly according to National Cancer Institute common toxicity criteria (9). Tumor measurements were obtained every 8 wk (two courses).

**Pharmacologic Studies.** Heparinized blood samples (5 ml) were collected at the end of infusion; at 1, 2, 5, 10, 20, 30, and 60 min; and at 2, 4, 6, 10, 24, and 48 h after the end of infusion. Urine was collected in timed aliquots for 48 h after administration. Hepsulfam concentrations in plasma and urine were measured by gas chromatography using a modification of a busulfan assay as previously described (10). Briefly, to each 1 ml of plasma or urine, 30 \( \mu \)l of the internal standard 1,8 bis(methanesulfonyloxy)octane (82 nmol) and 3 ml of ethyl acetate were added and mixed by gentle inversion for 2 min. Following centrifugation, the supernatant was removed, dried under nitrogen, resuspended in 200 \( \mu \)l of water:60 \( \mu \)l of 2,3,5,6-tetrafluorothiophenol (0.36 M);20 \( \mu \)l of sodium hydroxide (1.0 M), and heated overnight at 70°C. Then, 5 ml of sodium hydroxide (1.0 M) were added, and the mixture was vortexed. Next, 4 ml of hexane were added, the mixture was centrifuged for 10 min, and 200 \( \mu \)l of the hexane layer were diluted with 1200 \( \mu \)l of hexane. Two-\( \mu \)l samples of the hexane layer were injected into a Varian Model 3700 gas chromatograph (Varian, Palo Alto, CA). The gas chromatograph was fitted with a 6-ft x 2-mm (internal diameter) SP2250 80/100 Supelcoport column (Supelco, Bellefonte, PA) with nitrogen as the carrier gas at a flow rate of 30 ml/min. The injector was maintained at 250°C. The electron capture detector was maintained at 300°C. The column was temperature programmed from 230 to 250°C at 4°C/min. Under these conditions, the retention times of the derivatives of hepsulfam and the internal standard were 5.7 and 7.0 min, respectively. Hepsulfam concentrations were determined by comparing peak areas of hepsulfam with the internal standard. Calibration curves were run with each patient sample using pretreatment patient plasma to which 0 to 100 \( \mu \)l of hepsulfam (1 mmol/liter) had been added. The correlation coefficient exceeded 0.97 for all runs. The practical limit of this assay was 0.2 \( \mu \)mol/liter, and the coefficient of variation was 5.6% at 15 \( \mu \)mol/liter and 4% at 100 \( \mu \)mol/liter. Data were collected using Nelson 2600 Version 5.1 software (Perkin Elmer Nelson, Cupertino, CA). Concentrations were calculated using RS/1 software (BBN Software Products, Cambridge, MA). This assay should be specific for hepsulfam and should not measure the expected major metabolites of hepsulfam. The plasma hepsulfam concentrations for each patient were fit to a two-compartment model, and individual pharmacokinetic parameters were obtained using nonlinear regression analysis (PCNONLIN; Statistical Consultants, Lexington, KY). The AUCs were also calculated using the trapezoidal rule (11). Statistical analyses were carried out using standard parametric techniques (CSS; Statsoft, Tulsa, OK).

The pharmacokinetics and pharmacodynamics of hepsulfam were explored using a scatterplot of AUC versus the percentage of decrease in WBC, i.e.,

\[
100 \times \frac{\text{pretreatment WBC} - \text{nadir WBC}}{\text{pretreatment WBC}}
\]

This relationship was also modeled to a sigmoidal EMAX model (11).

\[
\% \text{ of change} = \frac{\text{maximum effect (AUC)\(_{\text{EMAX}}\)^2}}{\text{AUC}\(_{\text{050}}\)^2 + \text{AUC}\(_{\text{EMAX}}\)^2}
\]

Nonlinear least-squares regression using PCNONLIN was used to estimate \( K \), which describes the shape of the curve, and AUC\(_{\text{EMAX}}\) (AUC that produces 50% of the maximum effect). The maximum effect was assumed to be a 100% reduction in WBC count.

**RESULTS**

Patient characteristics are displayed in Table 1. Table 2 indicates the number of patients entered at each dose level, the number of patients in which dose escalations were performed, and the number of patients requiring dose reductions because of toxicity. Doses were escalated in only three patients, and doses were never increased by more than one level in any patient. Twenty-four of 53 patients (45%) received only a single course of hepsulfam due to either persistent drug toxicity and/or disease progression. Twenty-two patients received two courses, four patients received three courses, and only three patients received four or more courses of hepsulfam. Seven patients died prior to completion of a 28-day course of hepsulfam or before complete resolution of drug-related toxicity. Six of the seven patients died as a result of disease progression. One patient with an adenocarcinoma of the small intestine who received a single dose of 100 mg/m\(^2\) expired suddenly on Day 12 of therapy without any obvious evidence of drug-related toxicity. All patients entered are included in the toxicity data. No objective antitumor responses were observed.

**Hematological Toxicity.** Neutropenia and thrombocytopenia were the dose-limiting toxicities of hepsulfam administered on this schedule. Although toxicity of Grades 2 or greater was
Initially encountered at 100 mg/m², toxicity of this severity was not consistently seen thereafter even at the highest doses. Leukopenia and neutropenia were relatively mild in severity; however, the nadir counts were delayed in onset, and WBC depressions were protracted (Table 3). The median day of onset of hematological toxicity represents the first day of toxicity of any grade at each dose level. The median day of recovery from hematological toxicity represents the first day toxicity of any grade completely resolved. For neutropenia, the median day of onset was 22 days, and the median day of recovery was Day 44. Thrombocytopenia, albeit less common, was often more severe than leukopenia and demonstrated the same delay in onset (median, Day 22) and protracted time to recovery (median, Day 38; Table 3).

Grade 3 or 4 leukopenia occurred in only 3 of 95 courses and was not observed at hepsulfam doses < 100 mg/m². One patient treated at 100 mg/m² died prior to resolution of leukopenia after an aplasia lasting more than 42 days. One patient each treated at 270 mg/m² and 480 mg/m² had protracted leukopenia lasting more than 75 and 30 days, respectively. Similarly, Grade 3 or 4 thrombocytopenia (9 of 95 courses) was reversible in four patients at doses of 270 to 360 mg/m². However, in five patients who received doses ranging from 100 to 480 mg/m², it lasted longer than 60 days, including one patient treated at 480 mg/m² with thrombocytopenia lasting more than 200 days.

Hematological toxicity was not more common in extensively pretreated patients. Of the 32 extensively pretreated patients, 15 (47%) and 11 (34%) experienced leukopenia and thrombocytopenia, respectively. Of the 29 patients receiving more than one course of hepsulfam experienced thrombocytopenia. In 9 of these 11 patients, it was also cumulative as defined above.

A decrease in hemoglobin of greater than 1 gm/dl during a 28-day course of hepsulfam occurred in 18 patients. Neither the fall in hemoglobin nor the median day of nadir hemoglobin was clearly related to hepsulfam dose.

Nonhematological Toxicity. Elevations in serum aminotransferases were observed in 16 of 53 patients (Grade 1 in eight patients, Grade 2 in six patients, and Grade 3 in two patients). However, 12 of 16 patients were treated with relatively low doses (60 to 150 mg/m²), and 15 of the 16 patients had documented progression of liver metastases at the time of liver therapy.

4). Of the 29 patients who received more than one course of hepsulfam, 15 experienced leukopenia, and in 12 of the 15 patients, leukopenia was more severe by at least one grade or 1 wk longer in duration on the subsequent course. Eleven of the 29 patients receiving more than one course of hepsulfam experienced thrombocytopenia. In 9 of these 11 patients, it was also cumulative as defined above.

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Hepsulfam, a bifunctional alkylating agent, is of significant interest for several reasons. First, it is more active than busulfan in human and murine mammary tumor models in preclinical evaluations. Moreover, although it is closely structurally related to busulfan, data suggest that hepsulfam induces significantly more DNA interstrand cross-links than does busulfan after identical treatment durations in vitro (3, 5, 6). There are several important physicochemical differences between hepsulfam and busulfan that could explain these findings, including a distinct difference in the hydrolytic pattern of decomposition between the two agents. While busulfan is known to undergo an intramolecular displacement reaction after nucleophilic attack by water, this has not been demonstrated with hepsulfam (12). In addition, busulfan is capable of reacting with glutathione resulting in neutralization of its antitumor activity, whereas hepsulfam is unable to react with glutathione in either the presence or absence of glutathione transferases (12). Finally, hepsulfam is available as an i.v. formulation, whereas busulfan is only available as a p.o. formulation. This eliminates the direct gastrointestinal irritation caused by busulfan resulting in nausea, vomiting, and ultimately poor patient compliance. The i.v.

function test elevations, suggesting that these abnormalities were not due to hepsulfam.

Overall, minimal nonhematological drug-related toxicity occurred. Alopecia and rash were not observed. Nonhematological toxicities did not appear to be dose related and included Grade 1 mucositis (one course), nausea and vomiting (Grade 1 in three courses; Grade 2 in one course), malaise and fatigue (Grade 1 in three courses, Grade 2 in two courses). Pulmonary toxicity was not observed during any course of hepsulfam.

Pharmacokinetics. Complete plasma pharmacokinetic samples were collected during the first course of hepsulfam in 38 patients. The plasma disappearance of hepsulfam was best fit by a two-compartment model. The mean pharmacokinetic parameter values are listed in Table 5. Representative plasma elimination curves from a patient who received 210 mg/m² and a patient who received 270 mg/m² are shown in Fig. 2. The t_{1/2} and t_{max} after the doses administered in this study ranged from 1.9 to 77.8 min (mean, 18.9 min) and 1.4 to 16.2 h (mean, 5.5 h), respectively. Peak hepsulfam concentrations increased linearly with dose. The relationship of total-body clearance rate corrected for body surface area to dose was also linear. The volume of distribution at steady state ranged from 13.8 to 23.7 liters. The AUC increased linearly with dose. The fraction of drug excreted unchanged in urine was measured in 17 patients receiving 210 to 360 mg/m² and ranged from 1.6% to 12.6% (mean, 6.1%).

The relationship between AUC and changes in WBC was analyzed using a sigmoidal E_max model (11). Fig. 3 shows the scatterplot of AUC versus the percentage of change in WBC for all patients who had complete pharmacokinetic measurements during their first cycle of hepsulfam. The AUC_{50} was 7389 

\[ \text{AUC}_{50} = 7389 \] 

µmol-min/liter (95% confidence interval, 5165 to 9613), and \( K \) was 1.24 (95% confidence interval, 0.62 to 1.86). Because of the cumulative toxicity seen with multiple doses of hepsulfam, this model may underestimate the correlation between AUC and the percentage of change in WBC. In patients with hematological toxicity, AUC was also correlated with duration of thrombocytopenia \( (r = 0.78, P = 0.01) \). However, this correlation was limited due to the small number of patients who experienced hematological toxicity during their first course of hepsulfam.

DISCUSSION

Hepsulfam, a bifunctional alkylating agent, is of significant interest for several reasons. First, it is more active than busulfan in human and murine mammary tumor models in preclinical evaluations. Moreover, although it is closely structurally related to busulfan, data suggest that hepsulfam induces significantly more DNA interstrand cross-links than does busulfan after identical treatment durations in vitro (3, 5, 6). There are several important physicochemical differences between hepsulfam and busulfan that could explain these findings, including a distinct difference in the hydrolytic pattern of decomposition between the two agents. While busulfan is known to undergo an intramolecular displacement reaction after nucleophilic attack by water, this has not been demonstrated with hepsulfam (12). In addition, busulfan is capable of reacting with glutathione resulting in neutralization of its antitumor activity, whereas hepsulfam is unable to react with glutathione in either the presence or absence of glutathione transferases (12). Finally, hepsulfam is available as an i.v. formulation, whereas busulfan is only available as a p.o. formulation. This eliminates the direct gastrointestinal irritation caused by busulfan resulting in nausea, vomiting, and ultimately poor patient compliance. The i.v.

### Table 5 Mean pharmacokinetic parameters

<table>
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<th>Dose (mg/m²)</th>
<th>No. of patients</th>
<th>Peak concentration (µM)</th>
<th>α_{0} (min)</th>
<th>β_{0} (min)</th>
<th>Clearance (ml/min/m²)</th>
<th>( V_d ) (liter/m²)</th>
<th>AUC (µmol·min/liter)</th>
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* Mean ± SE.

### Fig. 2. Representative plasma elimination curves from two patients who received 150 mg/m² or 270 mg/m² of hepsulfam. Curve, fit of the data to a two-compartment model.

### Fig. 3. Percentage of change in WBC (100 × (pretreatment WBC – nadir WBC)/pretreatment WBC) in the first course of hepsulfam. Curve, fit of the data to a sigmoidal \( E_{max} \) model.
formulation will also potentially eliminate broad interindividual differences in bioavailability compared with busulfan, resulting in a more predictable toxicity pattern and antitumor efficacy. This may be particularly important with respect to severe busulfan-induced toxicities, such as hepatic venoocclusive disease, a major cause of morbidity with high-dose busulfan therapy which has been associated with high busulfan AUCs (7).

This Phase I and pharmacokinetic study of hepsulfam confirms toxicological and pharmacological observations obtained during preclinical evaluations. Minimal nonhematological toxicity was observed in this trial. The hepatic, central nervous system, and pulmonary toxicities seen with busulfan were not observed. Instead, the dose-limiting toxicities were leukopenia and thrombocytopenia. Hematological toxicity was delayed in onset, cumulative, and protracted. Although only a limited number of courses were associated with Grade 3 or 4 hematological toxicity, the toxicity was extremely protracted during some courses at doses above 210 mg/m² which most likely reflects the toxic effect of hepsulfam on hematopoietic stem cells. For this reason, a conventionally defined maximally tolerated dose producing consistent reversible Grade 3 myelosuppression could not be identified. These data strongly suggest that Phase II trials in patients with solid tumors should not utilize doses higher than 210 mg/m². This dose or higher doses may be well tolerated in leukemia patients. The prolonged time to recovery from myelosuppression after single doses, the high incidence of cumulative hematological toxicity, and the lack of data on patients receiving more than two doses at this level, which was largely due to protracted myelosuppression, argue against a higher starting dose. This pattern of hematological toxicity seen in both extensively pretreated and minimally pretreated patients would not permit the administration of successive courses as used in conventional Phase II trials. In addition, the mean peak hepsulfam concentration at the recommended starting dose of 210 mg/m² was 31 μM which may be suboptimal with respect to cytotoxicity. For example, this concentration is at least 4-fold lower than the minimal drug concentrations that are necessary in order to induce DNA interstrand and DNA-protein cross-linking and for cytotoxicity after 2 h of treatment in murine L1210 leukemia cells, two human leukemia cell lines, and two human colon carcinoma cell lines (5, 6). However, the peak concentration reached at the 210-mg/m² dose level is in the range of concentrations required to produce significant cytotoxicity (6 to 18 h of exposure) and DNA interstrand cross-linking (12 h of exposure) in peripheral blood cells from patients with chronic myelogenous leukemia (3).

Preclinical pharmacokinetic analysis of plasma drug elimination of hepsulfam showed a triphasic, dose-independent elimination pattern with half-lives ranging from 2 to 6 min (α phase), 58 to 96 min (β phase), and 7 to 15 h (γ phase). Hepsulfam was found to be rapidly taken up by RBC after bolus administration, and its concentration was found to slowly decline in whole blood to account for the slow terminal elimination phase (1). Pharmacokinetic data obtained during this trial did not demonstrate a protracted terminal half-life and did not fit a three-compartment model. In comparison, after p.o. administration, busulfan concentrations fit a one-compartment pharmacokinetic model with zero- or first-order absorption in both adult and pediatric patients (7, 8). Based on the data from this trial, the apparent maximal tolerated systemic exposure for hepsulfam without bone marrow support is in excess of 8000 μmol-min/liter (13). This level of exposure was reached by one of seven patients at 210 mg/m², two of four patients at 270 mg/m², and three of five patients at 360 mg/m², accounting for the prolonged neutropenia and thrombocytopenia. This exposure is equivalent to that produced by 4 to 8 mg/kg (160 to 320 mg/m²) of p.o. busulfan (7).

The lack of significant nonhematological toxicity of hepsulfam and its preclinical profile suggest that substantial dose escalation achieving relevant drug concentrations for antitumor effects might be feasible along with hematological stem cell support, such as autologous marrow transplantation or peripheral blood stem cell harvest and reinfusion. The delayed onset of leukopenia and thrombocytopenia observed with hepsulfam suggests a further advantage. With nadir counts occurring at Day 21, infusion of marrow or peripheral blood stem cells after hepsulfam administration could result in a relatively brief aplasia of only 7 to 10 days in duration prior to marrow engraftment and recovery of counts.

In summary, hepsulfam has several potential advantages over busulfan, including a broader spectrum of preclinical antitumor activity and availability in a parenteral formulation. In addition, it is associated with minimal nonhematological toxicity when administered as a single dose every 28 days. However, hepsulfam’s protracted myelosuppressive effects preclude traditional broad Phase II trials in solid tumor patients requiring repetitive dosing or dose escalation outside the setting of bone marrow stem cell support. Higher doses may be tolerated in leukemia patients, and higher drug exposure times may be achieved in these patients.

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**REFERENCES**

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