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ORIGINAL ARTICLE

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Encephalopathy is the dose-limiting toxicity of intravenous hepsulfam: results of a phase I trial in patients with advanced hematological malignancies

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Abstract Hepsulfam is a bisulfamic ester which is similar in structure to busulfan and is believed to act as a bifunctional alkylator inducing both DNA–DNA and DNA–protein crosslinks. Prior studies in patients with refractory solid tumors have identified the dose-limiting toxicity of hepsulfam to be cumulative myelosuppression resulting in prolonged leukopenia and thrombocytopenia. This phase I trial was designed to determine the maximally tolerated dose of hepsulfam administered intravenously in patients with refractory leukemias and other advanced hematologic malignancies. Hepsulfam was administered as a 30-min or 2-h intravenous infusion to 21 patients with advanced leukemia or multiple myeloma. All patients had been extensively treated and had progressive disease. Cycles were repeated every 5 weeks. Cohorts of patients were treated at 360, 480, 640, and 800 mg/m^2. The dose-limiting toxicity of intravenous hepsulfam was severe encephalopathy. The single patient treated at 800 mg/m^2 became comatose within 48 h and required 3 weeks for his mental status to return to baseline. There were, however, no irreversible neurological sequelae. Several patients treated at 640 mg/m^2 had clinical evidence of toxic deliriums and slowing of alpha rhythm waves on electroencephalograms indicative of a gray-matter encephalopathy. When hepsulfam was infused over 30 min, patients complained of uncomfortable parasthesias, but when the drug was administered over 2 h, these acute symptoms were less common. Myelosuppression was observed in most patients. Among those patients who had some suppression of their leukemia, peripheral blood counts recovered to pretreatment levels after 3–5 weeks. Apart from CNS toxicity, non-hematologic toxicity was minimal. Pharmacokinetic studies demonstrated rapid clearance of hepsulfam so that the drug was not reliably detected in the plasma after 24 h. The recommended phase II dose of hepsulfam as a single 2-h intravenous infusion is 480 mg/m^2, but this dose provided relatively little clinical benefit for patients with refractory leukemia. The dose-limiting toxicity is CNS toxicity with increasingly severe encephalopathy at doses $\geq$ 640 mg/m^2. It would be reasonable to investigate further dose escalation of hepsulfam in a divided dose schedule to minimize the peak concentrations which may be related to the encephalopathy. EEG monitoring is recommended for early detection of slowing of alpha rhythm waves. Hematopoietic stem cell support will probably be required at total doses exceeding 800 mg/m^2.

Key words Encephalopathy · Hepsulfam · Acute leukemia

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Introduction

Hepsulfam (sulfamic acid diester; NSC 329680) is a new compound which has been developed by the Division of Cancer Treatment of the National Cancer Institute as an active neoplastic agent, based upon its high degree of activity against multiple murine tumors in vivo, as well as in tumor assay models [3]. Compared to its parent compound busulfan, hepsulfam demonstrates

much greater activity in five tumor models including L1210 and P388 leukemias, mammary carcinoma and an implanted B12 melanoma line. Hepsulfam is a bisulfamic ester which is similar in structure to busulfan and is believed to act as a bifunctional alkylator, inducing both DNA–DNA and DNA–protein crosslinks [8, 9]. Thus far, there have been two phase I studies in patients with refractory solid tumors, one at the Johns Hopkins Oncology Center and the other at the University of Texas Health Science Center in San Antonio, Texas [6, 10]. Patients received initial doses of 30 mg/m^2, and doses were escalated in cohorts to 480 mg/m^2. Dose-limiting toxicity was cumulative myelosuppression resulting in both prolonged leukopenia and thrombocytopenia. In addition, hepsulfam has been shown to be more effective than busulfan in inhibiting myeloid colony-forming units cultured in vitro from mononuclear blood cells from patients with chronic myelogenous leukemia (CML) [7]. Because of this toxicity spectrum, we felt that this drug could be an active agent in patients with leukemia or other advanced hematologic malignancies and eventually for patients undergoing bone marrow transplantation.

The purpose of this phase I trial was to determine the maximally tolerated dose of hepsulfam administered intravenously in patients with refractory leukemias and to describe and quantitate the toxicity of hepsulfam in this patient population. We also measured plasma drug levels to determine whether delayed elimination of hepsulfam occurs in this patient population. This would be very important if hepsulfam were to be used as a chemopreparative agent for bone marrow transplantation. We studied the possible therapeutic activity of this drug in this particular group of patients with advanced hematological malignant diseases.

Materials and methods

Patient population

Patients were eligible for this study if they were older than 18 years and had a performance status of > 60% (Karnofsky). One of the following diagnoses was required to be present: refractory acute leukemia, defined as a patient with either acute myeloid or lymphoblastic leukemia (AML or ALL) who failed to enter complete remission with either conventional or high-dose induction therapy and who was not a candidate for allogeneic bone marrow transplantation; patients with either AML or ALL who had relapsed and were not considered candidates for either allogeneic or autologous bone marrow transplantation; patients with CML in either accelerated or blast phase; patients with advanced myelodysplastic syndromes for whom there is no conventional therapy; or patients with advanced refractory chronic lymphocytic leukemia, prolymphocytic leukemia, myeloma, or advanced stage lymphomas. All patients signed a consent form approved by the University of Chicago Clinical Investigations Committee (IRB) and by the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute.

Exclusion criteria included abnormal hepatic function (bilirubin > 2.0 mg/dl, SGOT or alkaline phosphatase more than three times normal unless due to leukemia infiltration of the liver), abnormal renal function (creatinine > 2.0 mg/dl or creatinine clearance of < 30 ml/min), or other significant medical or allergic disorders which would make administration of hepsulfam hazardous or obscure interpretation of various effects. Additionally, patients could not have received radiotherapy, chemotherapy, or immunotherapy within 4 weeks of proposed treatment. Female patients of childbearing age were requested to take appropriate measures to avoid pregnancy and must have had a negative pregnancy test.

Within 2 weeks of the start of therapy, patients were required to have a complete history and physical examination. Laboratory screening included a complete blood count with differential and platelet counts, bone marrow aspiration and biopsy within 2 weeks prior to starting the trial, chemistry profile, chest radiograph, electrocardiogram, urinalysis, prothrombin time and partial thromboplastin time, creatinine clearance, and pregnancy test for females.

Additionally, a baseline electroencephalogram (EEG) was required within 1 week of first treatment with hepsulfam for the final four patients entered into this study. Scalp electrodes were applied according to the 10–20 system, and an EEG was recorded using a 21-channel Nihon Kohden EEG machine. EEG recordings were made using a parasagittal montage and performed when the patient had eyes closed and was judged clinically to be most alert. For power spectra determinations, the EEG was digitized at 202 Hz and the power spectra calculated using software provided by Stellate Systems (Montreal, Canada). The pre and posttreatment EEG power spectra were compared by calculating a score, Θ, from the power in the different frequency bands, where Θ = (alpha + theta)/delta.

Dosage and formulation:

Hepsulfam was supplied by the Division of Cancer Treatment (DCT) of the National Cancer Institute as a sterile vacuum-dried powder with 150 mg in 10 ml vials. Also provided was an ampoule containing 5 ml of special diluent for use in reconstituting the product. The diluent had the following composition: ethanol 10% (v/v), propylene glycol 40%, pH 7.5, and 0.05 ml phosphate buffer. The final solution of hepsulfam after reconstitution contained 30 mg/ml. The hepsulfam was further diluted with 200 ml 5% dextrose in water or with normal saline) for administration.

The intact packages of hepsulfam were stored under refrigeration at 4°C. The solution reconstituted in the special diluent reportedly retains at least 90% hepsulfam potency for at least 6 days at room temperature [3]. When the reconstituted solution was diluted tenfold with normal saline or 5% dextrose to a concentration of 3 mg/ml, the solution retained at least 90% hepsulfam potency for 24 h at room temperature. However, the single-use vacuum-dried storage form of hepsulfam contained no antibacterial preservative. Therefore, the reconstituted product was discarded 8 h after initial entry.

Treatment plan

Patients received an intravenous infusion, initially over 30 min and later over 2 h, either in the hematology outpatient clinic or in the inpatient hematology/oncology unit at the University of Chicago Medical Center.

Based upon previous phase I study results, the first cohort of patients was started at a dose of 360 mg/m^2. A minimum of three patients were evaluated at each nontoxic dose level. Four dose levels were explored: 360, 480, 640, and 800 mg/m^2. Patients were eligible for a second infusion at the same dose if there was no evidence of disease progression and toxicity had resolved after 5 weeks. Dose escalation was not permitted within the same patient.

Follow-up

Patients remained under close observation for at least 2 h following the first dose. In general, patients were also evaluated on the day following infusion and then every other day when they returned to clinic to have blood drawn. Patients were examined weekly while in the study. A complete blood count, differential and platelet counts, and chemistry panel were obtained weekly. Bone marrow aspiration and biopsy were carried out on days 7, 21, and 35, if possible, following treatment. Repeat EEGs were obtained within 5 days of hepsulfam treatment and again for any sign of central nervous system (CNS) toxicity in the final four patients studied. Cerebrospinal fluid (CSF) was obtained by lumbar puncture when clinically indicated. Toxicity was graded according to the NCI Common Toxicity Criteria.

Pharmacokinetic analyses

Blood samples were obtained from each patient starting 1 day after the hepsulfam infusion, and then every second day thereafter (approximately days + 1, + 3, + 5, + 7, + 9, and + 11). The plasma was separated, frozen at − 20°C, and subsequently analyzed by gas chromatography [2, 6]. The detection limit of this method is > 0.3–0.5 μ*M*. The drug remains stable in plasma at − 20°C for longer than 6 months.

Results

Nine males and 12 females were entered into this study. Their median age was 47 years (range 18–66 years). Of the 21 patients, 14 had refractory AML, 3 had ALL, 3 had CML in blast phase, and 1 had multiple myeloma. All had been extensively treated, and 3 patients had relapsed following bone marrow transplantation.

Three patients were treated at 360 mg/m^2, 6 at 480 mg/m^2, 11 at 640 mg/m^2 and 1 at 800 mg/m^2. All patients were evaluable for toxicity. At these doses, most (but not all) patients showed a significant decrease in peripheral blast counts with an accompanying decrease in bone marrow cellularity and blast cell percentages (Table 1). The clinical benefits, however, were of short duration, and only 2 patients received more than one course. One 47-year-old woman with CML in blast phase responded to 360 mg/m^2 with a morphologic conversion to chronic phase CML in her bone marrow after her initial treatment. She subsequently received 11 courses of hepsulfam approximately every 5–6 weeks and continued to show a response after each dose lasting about 4 weeks, until her blast cells again became predominant. She withdrew from treatment after 12 months, having received a cumulative dose of 3960 mg/m^2 of hepsulfam. She expired from progressive leukemia 6 weeks later. One other patient with refractory AML received three courses of therapy (480 mg/m^2) with a marked decrease both in peripheral blast cell counts and in marrow cellularity for two courses and then progression. No cumulative toxicity was noted in either patient. No other patient received more than one course of hepsulfam, generally because of lack of clinical benefit.

Table 1. Myelosuppression after hepsulfam (*DR* disease-related)

Dose (mg/m^2)	Patient no.	Diagnosis	WBC ($\times 10^3/\mu l$) Pretreatment	WBC ($\times 10^3/\mu l$) Nadir (day)	Platelets ($\times 10^3/\mu l$) Pretreatment	Platelets ($\times 10^3/\mu l$) Nadir (day)	Recovery
360	201	AML	4.5	0.9 (18)	17	8 (15)	No (DR)
	202[a]	CML-BP	17.2	2.4 (13)	62	38 (8)	Day 29
	203	AML	2.1	0.9 (14)	20	12 (9)	No (DR)
480	204[a]	AML	17.9	0.4 (13)	291	95 (29)	Day 36
	205	AML	16.2	6.8 (8)	100	52 (8)	Day 15
	206	AML	6.0	1.6 (9)	25	5 (20)	No (DR)
	207	ALL	22.8	1.1 (15)	13	8 (8)	No (DR)
	220	AML	113.5	None[b]	42	33 (4)	No (DR)
	221	CML-BP	3.4	3.0 (4)	30	8 (13)	No (DR)
640	208	AML	1.0	0.4 (7)	6	12 (23)	No (hypocellular BM)
	209	AML	93.1	5.2 (8)	17	11 (8)	No (DR)
	210	AML	1.0	0.6 (12)	150	13 (14)	Day 57
	211	CML-BP	9.8	0.4 (23)	134	2 (21)	No (DR)
	212	ALL	2.6	None[b]	136	103 (8)	No (DR)
	213	ALL	29.7	0.3 (9)	17	11 (14)	No (DR)
	214	AML	40.8	0.6 (13)	42	14 (9)	No (DR)
	215	AML	1.0	0.1 (10)	6	2 (4)	No (DR)
	216	AML	40.2	0.3 (12)	53	12 (14)	No (DR)
	218	AML	24.0	5.1 (10)	66	26 (10)	No (DR)
	219	AML	18.7	0.8 (12)	28	12 (7)	No (DR)
800	217	Myeloma	4.4	0.2 (14)	293	11 (14)	No (hypocellular BM)

[a]First course only
[b]The WBC count never decreased after treatment

Neurotoxicity

At the 640 mg/m^2 dose level, several patients complained of uncomfortable paresthesia in their extremities during or shortly after the 30-min hepsulfam infusion. In each case, these resolved after slowing or temporarily suspending the infusion. This acute symptom has not been previously reported with hepsulfam but may possibly be due to either the high peak concentration of hepsulfam or the propylene glycol present in the diluent (2 ml/150 mg hepsulfam). In preclinical studies, ataxia, convulsions, lethargy, and tremors have been noted in rats treated at the highest dose level tested (1.5 times the single dose lethal to 10% of mice; 1.5 $MELD_{10}$) as well as in vehicle-treated control animals [3]. Therefore, the protocol was amended to increase the infusion period from 30 min to 2 h. Several additional patients were then treated without any acute peripheral neuropathic symptoms, although one patient appeared agitated and short of breath approximately 1 h and 40 min into the 2-h infusion. His symptoms resolved quickly after discontinuation of the infusion which was completed approximately 30 min later.

In addition, several patients treated in the cohort receiving 640 mg/m^2 reported somnolence, slurred speech, ataxia, and paresthesias beginning 1–3 days after the hepsulfam infusion and persisting for several days before resolving completely. This symptom has not been previously reported with hepsulfam. Prompt recognition of these drug-related symptoms was sometimes made difficult by concomitant use of antinausea, anxiolytic, or analgesic medications by these patients.

It now appears that severe CNS toxicity is the dose-limiting toxicity for hepsulfam, based upon our experience with a single patient treated at 800 mg/m^2. Although no acute symptoms were experienced by this patient during the infusion, within 24 h of treatment, he had confusion and disorientation. The CNS toxicity progressed to coma within the next 24 h from toxic encephalopathy, and possible seizure activity was present. Treatment with antiepileptic drugs, mechanical ventilation and two blood-volume exchanges were performed over the next 10 days. Serial EEGs documented the gray-matter encephalopathy. CSF examinations were unremarkable except for elevated protein levels. Over 3 weeks, this patient's mental status returned to baseline, and there appeared to be no significant neurological sequelae. For this reason, the protocol was amended to require a baseline EEG within 1 week of first treatment with hepsulfam and a repeat EEG 2–5 days after hepsulfam treatment and again for any signs of CNS toxicity. The dose of hepsulfam was de-escalated to 640 mg/m^2, and two additional patients were treated. When EEG and clinical evidence of encephalopathy was observed in both of these patients, the hepsulfam dose was lowered further to 480 mg/m^2 and two final patients were studied. It was decided not to treat any additional patients at the 800 mg/m^2 dose level because of the severe grade 4 neurotoxicity experienced by the single patient treated at this level. In addition, this patient experienced severe myelosuppression (aplasia) which did not improve during the remainder of his life (2.5 months).

EEG monitoring was performed on the last four patients treated with hepsulfam (Table 2). A significant dose-related slowing of the alpha rhythm waves was recorded in the two patients treated at 640 mg/m^2 indicative of a mild gray-matter encephalopathy, but seizure activity was not observed. Figure 1 shows segments of the EEG recorded from right parietal-occipital regions (P4-02) in these patients pre- and post-treatment. At 480 mg/m^2, hepsulfam did not produce a significant alteration in EEG background ($\Theta > 3$). However, at a dose of 640 mg/m^2, hepsulfam resulted in a slowing of the background ($\Theta < 3$) consistent with a mild to moderate gray-matter encephalopathy. These EEG changes were mirrored clinically by toxic deliriums (mild in patient 218; severe in patient 219). Epileptiform activity was not recorded by EEG and no seizures were observed clinically. Magnetic resonance imaging was not performed.

Hematological toxicity

Myelosuppression was observed in most patients, many of whom had peripheral blood cytopenias prior to treatment because of progressive bone marrow disease. The pattern of myelosuppression (pancytopenia) suggests toxicity to stem cells. Typically, the nadirs for neutrophils and platelets were observed 1–2 weeks after treatment with hepsulfam (Table 1). This also coincided with maximum leukemia cell reduction in blood and marrow samples. Recovery of blood counts back to baseline levels was observed 4–5 weeks after treatment in those patients who had some suppression of their leukemia. Several patients treated at 640 mg/m^2 continued to demonstrate severe hypocellularity in bone marrow biopsies with small amounts of residual leukemia. The one patient who received

Table 2 EEG alpha rhythm

Patient no.	Dose (mg/m^2)	Pre-hepsulfam	Post-hepsulfam	Symptoms
220	480	9–10 Hz	9–10 Hz	None
221	480	9–10 Hz	9–10 Hz	None
218	640	10–11 Hz	8–9 Hz	Mild delirium
219	640	8–9 Hz	6–7 Hz	Severe delirium

800 mg/m^2 started with normal blood counts despite 53% myeloma in his marrow. After treatment, he was left with minimal hematopoiesis plus small amounts of residual multiple myeloma in the marrow.

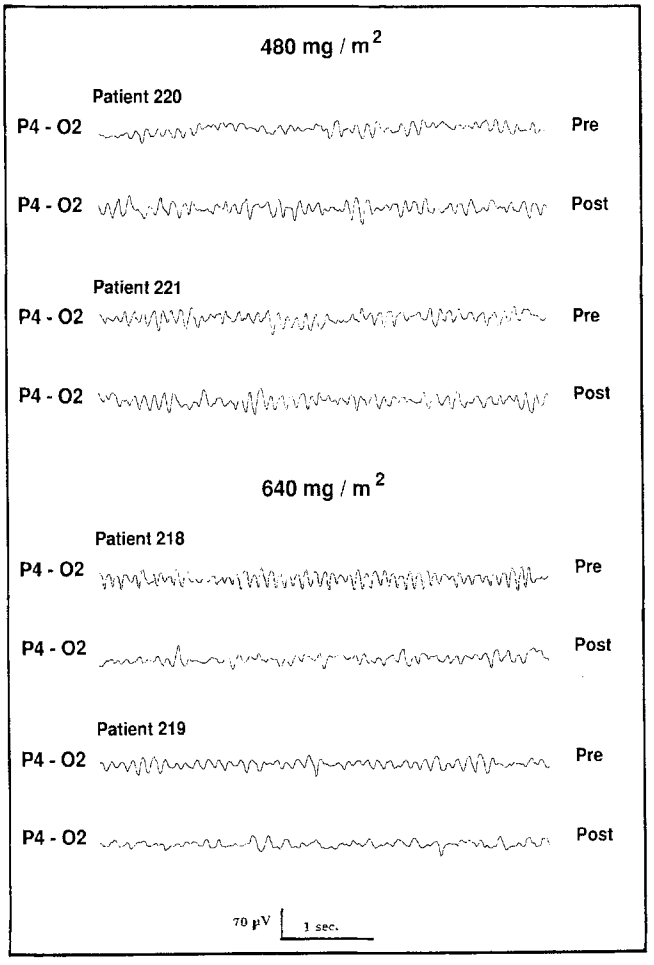

Fig. 1 Representative EEG tracings from right parietal-occipital regions for patients prior to taking hepsulfam and after receiving treatment. The EEG segments were recorded when the patient was judged clinically to be most alert. This EEG electrode pair was chosen since for most normal individuals, there is higher amplitude alpha activity on the right side [11]

Apart from CNS toxicity, non-hematologic toxicity was minimal (Table 3).

Drug levels

The measured plasma hepsulfam concentrations are shown in Table 4. In general, the drug was not reliably detected after the 24-h level. Peak concentrations after the 2-h infusions were 18–22 μM at 480 mg/m^2 ($n = 2$) and 29–44 μM at 640 mg/m^2 ($n = 3$).

Discussion

Hepsulfam, like busulfan, is an alkylating agent that induces DNA crosslinks and DNA protein crosslinks. It is of considerable interest for several reasons. First, hepsulfam appears more active than busulfan in human and animal tumor models [3, 7]. Unlike busulfan, which induces predominantly DNA intrastrand crosslinks, hepsulfam induces predominantly interstrand crosslinks [7–9]. The hydrolytic pattern of decomposition also differs between the two agents. Busulfan is known to undergo an intramolecular displacement reaction after nucleophilic attack by water, but this has not been demonstrated with hepsulfam [1, 5]. In addition, glutathione reacts with busulfan neutralizing its antitumor activity, whereas hepsulfam is unable to react with glutathione in either the presence or absence of glutathione transferases [1, 12]. The plasma half-life of busulfan is 2–3 h in contrast to about 16 h for hepsulfam [3–6]. Finally, hepsulfam is available as an intravenous formulation while busulfan is only available as an oral drug. Thus, the intravenous formulation may potentially reduce the broad interindividual differences in bioavailability which have been demonstrated with busulfan, resulting in a more predictable pattern of toxicity and antitumor effect [2, 4].

Preclinical pharmacokinetic analyses of hepsulfam elimination from plasma showed a triphasic, dose-independent elimination pattern with half-lives ranging

Table 3. Severe or greater non-hematological toxicities after hepsulfam

Dose (mg/m^2)	Patient no.	Grade 3	Grade 4
360	202	Fever (40.2°C)	
480	206	Gram-negative infection	
	207[a]		Bilirubin 4.8 mg/dl Creatinine 7.7 mg/dl
640	208	Infection	Gastrointestinal bleeding
	213	Dysrhythmia, ataxia	
	215	Neurocortical	Fungal pneumonia
	218	Neurocortical	
	219	Neurocortical	
800	217	Supraventricular tachycardia, infection	Neurocortical, infection

[a] Grade 4 toxicities coincided with antibiotic treatment of a febrile episode

Table 4. Plasma hepsulfam concentration (μM) (*ND* hepsulfam not detected reliably at concentrations < 0.3–$0.5\ \mu M$

Dose (mg/m^2)	Patient no.	Peak	Day + 1	Day + 3	Day + 5
360	201		4.1	ND	
	202		ND		ND
	203		1.9		ND
480	204		0.8		0.7
	205		0.6		ND
	206		0.5	0.7	
	207		1.4	0.8	
	220	17.5	0.6	ND	ND
	221	21.8	0.8	0.4	
640	208		2.9	0.4	
	210		1.1	0.4	
	211		1.4	ND	
	212		5.9	ND	
	213		1.4		
	214		0.4	ND	ND
	215		1.2		ND
	216	37.1			ND
	218	28.6	1.0	0.4	
	219	43.9	1.6	ND	ND
800	217		0.5	ND	ND

from 2 to 6 min for the alpha phase, 58 to 96 min for the beta phase, and 7 to 15 h for the gamma phase [3]. Hepsulfam was rapidly taken up by red blood cells after bolus administration and its concentration was found to slowly decline in whole blood and plasma. The terminal plasma and blood half-lives in humans have been reported to be 15.9 ± 4.6 and 90 ± 13 h, respectively [10]. A phase I trial in patients with solid tumors has shown that the plasma disappearance of hepsulfam is best fit by a two-compartment model [6]. The half-lives for the doses administered in that study ranged from 2 to 78 min for the alpha phase (mean 19 min) and 1.4 to 16.2 h for the beta phase (mean 5.5 h). Peak hepsulfam concentrations increased linearly with dose. In patients with hematological toxicity, the area under the curve was significantly correlated with duration of thrombocytopenia. No attempt was made in the current study to correlate myelosuppression with plasma concentration of hepsulfam because of the severely and variably compromised bone marrow function of the patients treated.

The lack of significant non-hematological toxicity of hepsulfam suggests that substantial dose escalation might be feasible along with hematological stem cell support such as that provided by autologous marrow transplantation or peripheral blood stem cell reinfusion. The delayed onset of leukopenia and thrombocytopenia observed with hepsulfam suggests a further advantage. Since nadir counts occur during the second and third week after treatment, a relatively brief period of pancytopenia would be anticipated prior to marrow engraftment and recovery of blood counts. Unfortunately, further dose escalation of single doses of hepsulfam does not appear feasible due to the encephalopathy that we observed and which may be related to peak concentration. In particular, the patient with the most neurotoxicity at the 640 mg/m^2 dose level also had the highest measured peak hepsulfam concentration.

The recommended phase II dose of hepsulfam as a single 2-h IV infusion is 480 mg/m^2, but this dose had relatively little clinical benefit for patients with refractory leukemia. The antileukemia response was rarely sustained. The dose-limiting toxicity is CNS toxicity with increasingly severe encephalopathy at doses ≥ 640 mg/m^2. Irreversible marrow aplasia occurred in the single patient treated at 800 mg/m^2. Rapid metabolism and/or elimination occurred so that hepsulfam was not reliably detected in plasma at 48 h. It would be reasonable to investigate further dose escalation of hepsulfam in a divided-dose schedule to minimize the peak concentrations. An appropriate trial could begin at 160 mg/m^2 per day for 4 days. EEG monitoring is recommended for early detection of slowing of the alpha rhythm. Serial cognitive function testing should also be performed to evaluate long-term sequelae. Blood or marrow stem cell support is probably required at doses exceeding 200 mg/m^2 per day for 4 days. Patients with advanced hematological malignancies who had had hematopoietic stem cells cryopreserved while in remission would be appropriate candidates for such a trial.

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