**Purpose:** A phase I trial of intrathecal Spartaject Busulfan (SuperGen, Inc., San Ramon, CA) was conducted in children with neoplastic meningitis following recurrent primary brain tumors to describe toxicities, estimate the maximum tolerated dose (MTD), and document evidence of responses to this agent.

**Experimental Design:** The continuous reassessment method was used to assign cohorts of patients to doses of intrathecal Spartaject Busulfan via an Ommaya reservoir and/or lumbar puncture twice weekly for 2 weeks followed by an assessment of toxicity and response. Patients with stable disease or an objective response continued to receive intrathecal Spartaject Busulfan plus systemic chemotherapy at regular intervals. Cerebrospinal fluid and blood were obtained for pharmacokinetic studies in patients with Ommaya reservoirs after the first dose of intrathecal Spartaject Busulfan. Seven evaluable patients were assigned to the starting dose of 5 mg, two patients to 7.5 mg, three patients to 10 mg, seven patients to 13 mg, and four patients to 17 mg.

**Results:** Between September 2000 and May 2003, 28 patients were enrolled in this study. Twenty-three patients (median age, 8.8 years; range, 2.5-19.5 years) were evaluable for estimating the MTD, and dose-limiting toxicities were observed in three and included grade 3 vomiting (n = 1 at 5 mg), grade 3 headache (n = 1 at 17 mg), and grade 3 arachnoiditis (n = 1 at 17 mg). Pharmacokinetic data showed that post-infusion concentrations of busulfan ranged from 50 to 150 μg/mL and declined to <1 μg/mL within 5 hours.

**Conclusions:** Intrathecal Spartaject Busulfan was well tolerated in children with neoplastic meningitis from brain tumors, and the recommended dose for future phase II studies is 13 mg.

The leptomeninges are a frequent site of dissemination in children with malignant brain tumors, occurring in up to 20% of patients at the time of diagnosis or progression (1, 2). Leptomeningeal disease occurs more frequently in children with primitive neuroectodermal tumors but may also occur in children with ependymoma, germ cell tumors, or malignant gliomas (1, 2). Patients with leptomeningeal disease at initial diagnosis are usually treated with neuraxis irradiation. The addition of systemic chemotherapy for such patients seems to be beneficial for only those with primitive neuroectodermal tumors and germ cell tumors (3, 4). Treatment for patients with tumor dissemination to the cerebrospinal fluid (CSF) and leptomeninges at the time of disease progression is generally unsatisfactory and carries a poor prognosis. Administration of chemotherapy directly into the intrathecal space (via a lumbar puncture or a reservoir placed in one of the lateral ventricles) has been used for several years to prevent central nervous system disease in patients with leukemia or lymphoma or treat leptomeningeal disease from both primary or secondary brain tumors (5, 6). There are several advantages to this method of delivery (6). Because the total volume of CSF is only 150 mL even in an adult, high CSF concentrations of a drug can be achieved even with small doses and thereby minimize systemic toxicity. In addition, because the CSF has intrinsically low levels of enzymes, drugs injected into this compartment are not degraded easily and may have a longer half-life compared with the systemic route. In addition, due to the low protein levels in the CSF, there is more unbound drug available for diffusion into the extracellular space of the brain (6).

The only standard anticancer agents currently available for intrathecal administration are methotrexate, cytosine arabinoside, and thiopeta (6). Therefore, there is an imperative need for developing newer agents for treatment of leptomeningeal
disease in children with recurrent primary brain tumors. Busulfan is an alkylating agent that has been used in the treatment of chronic myelogenous leukemia and in high-dose chemotherapy schedules for allogenic and autologous bone marrow transplantation in patients with leukemias and solid tumors (7, 8). This alkylating agent has shown efficacy in preclinical studies using medulloblastoma, ependymoma, and malignant glioma xenografts with no demonstrable cross-resistance with other agents, including cyclophosphamide and melphalan (9, 10). Busulfan has previously been available only in an oral formulation that is poorly water soluble and hence not suitable for parenteral administration. Recently, a watersoluble microcrystalline formulation of Busulfan (Spartaject Busulfan, SuperGen, Inc., San Ramon, CA) became available for experimental use (11). This agent has been found to be active in a nude rat model of human neoplastic meningitis and safe following intrathecal injection in nonhuman primates7 and adult patients with leptomeningeal disease (12, 13). The results of these studies formed the basis for initiating a phase I trial of intrathecal Spartaject Busulfan in children with leptomeningeal disease from recurrent or progressive primary brain tumors. We now report the results of this study describing the toxicities, maximum tolerated dose (MTD), pharmacokinetics (CSF and plasma), and preliminary evidence of effectiveness of this agent in this patient population.

### Materials and Methods

This phase I study was conducted at nine member institutions of the pediatric brain tumor consortium (see Appendix 1). The study was open for enrollment in July 2000 and permanently closed for accrual in May 2003. **Study aims.** The primary aims of the study were (a) to estimate the MTD of intrathecal Spartaject Busulfan using a limited dosage escalation schedule; (b) to assess the qualitative and quantitative toxicities of intrathecal Spartaject Busulfan when administered to children and adolescents with leptomeningeal disease from recurrent or progressive primary brain tumors; (c) to estimate the CSF and plasma pharmacokinetics of intrathecal Spartaject Busulfan administered via the intraventricular and lumbar routes; and (d) to obtain preliminary information about the efficacy of this agent.

**Eligibility criteria.** Eligibility criteria for this study were (a) age ≥2 and ≤21 years; (b) presence of a primary malignant brain tumor refractory to standard therapy and metastatic to CSF and/or leptomeningeal subarachnoid space as determined by CSF cytology and/or neuroimaging evidence of leptomeningeal disease; (c) Karnofsky or Lansky status of ≥50% and life expectancy of at least 8 weeks; (d) evidence of recovery from prior therapy 3 weeks from prior systemic chemotherapy (6 weeks for nitrosoureas), 1 week from prior intrathecal chemotherapy (2 weeks for liposomal cytarabine), 1 week from prior focal radiotherapy, and 8 weeks from prior craniospinal irradiation; (e) adequate organ function, including an absolute neutrophil count >1,000/mm³, platelets ≥75,000/mm³, serum creatinine <1.5 times normal for age, serum bilirubin within normal limits for age, serum transaminases (alanine aminotransferase/aspartate aminotransferase) <5 times normal for age, and no overt evidence of cardiac, pulmonary, or renal disease; (f) adequate CSF circulation as shown by a ¹¹¹Indium-labeled or ⁹⁹Technetium-labeled diethylaminoethylpentaoctetate acid CSF flow study obtained following a lumbar puncture; and (g) signed informed consent according to institutional guidelines. Patients excluded from this study were those with CSF obstruction or compartmentalization, concomitant bone marrow disease, and uncontrolled infection. Focal radiotherapy was allowed within 2 weeks of treatment to improve CSF flow in those with CSF obstruction, but a repeat CSF flow study was required to confirm adequate CSF circulation before enrollment. Patients who were pregnant or breastfeeding were also excluded from the study.

### Table 1. Dose levels and observed DLT in 23 patients with leptomeningeal disease from primary brain tumors treated with intrathecal Spartaject Busulfan

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Age ≥3 y</th>
<th>Age &lt;3 y</th>
<th>No. patients treated</th>
<th>Observed DLT (no. patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 mg</td>
<td>4 mg</td>
<td>7</td>
<td>Grade 3 emesis (1)</td>
</tr>
<tr>
<td>2</td>
<td>7.5 mg</td>
<td>6 mg</td>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>10 mg</td>
<td>8 mg</td>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>13 mg</td>
<td>10 mg</td>
<td>7</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>17 mg</td>
<td>14 mg</td>
<td>4</td>
<td>Grade 3 headache, arachnoiditis (2)</td>
</tr>
</tbody>
</table>

*Only one patient was <3 y of age at the time of enrollment.

### Table 2. Clinical characteristics of 23 patients with leptomeningeal disease from primary brain tumors treated with intrathecal Spartaject Busulfan

<table>
<thead>
<tr>
<th>Total no. patients</th>
<th>23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at study entry (range)</td>
<td>8.8 y (2.5-19.5)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>18/5</td>
</tr>
<tr>
<td>No. patients with ventriculoperitoneal shunts</td>
<td>7</td>
</tr>
<tr>
<td>LMD by MRI scan of brain and spine</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>4</td>
</tr>
<tr>
<td>Brain + spine</td>
<td>14</td>
</tr>
<tr>
<td>Spine</td>
<td>3</td>
</tr>
<tr>
<td>None*</td>
<td>2</td>
</tr>
<tr>
<td>CSF cytology</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>14</td>
</tr>
<tr>
<td>Negative</td>
<td>8</td>
</tr>
<tr>
<td>Not available</td>
<td>1</td>
</tr>
<tr>
<td>Tumor histology</td>
<td></td>
</tr>
<tr>
<td>PNET</td>
<td>15</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>4</td>
</tr>
<tr>
<td>Malignant glioma</td>
<td>3</td>
</tr>
<tr>
<td>Choroid plexus carcinoma</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: LMD, leptomeningeal disease; PNET, primitive neuroectodermal tumor.

*Two patients had positive CSF cytology without LMD per neuroimaging.
Spartaject Busulfan. Spartaject Busulfan was supplied by SuperGen as a lyophilized powder in single-use, 10-mL vials each containing 25 mg. Spartaject Busulfan is a formulation in which drug is encapsulated in a mixture of phospholipids, dimyristoylphosphatidylcholine, and dilauroylphosphatidyl choline in a buffer containing mannitol at a pH of 6.5. The lyophilized, sterile product was reconstituted with 10 mL of sterile water for injection to form a sterile suspension with a concentration of 2.5 mg/mL, with a pH between 5.5 and 6.5. The appropriate dose of reconstituted drug was made up to a final volume of 10 mL with preservative-free, pyrogen free normal saline and administered (unfiltered) within 8 hours of reconstitution.

Treatment plan. Spartaject Busulfan was delivered intrathecal via Ommaya reservoir, lumbar puncture, or lumbar reservoir. For patients with Ommaya reservoirs, treatment was alternated between intraventricular and intralumbar sites. Patients initially received two treatments a week, at least 3 days apart for 2 weeks. Patients with ventriculoperitoneal shunts (n = 7) were treated through the lumbar route only. Those with an objective response or stable disease at the initial evaluation after 2 weeks (four doses) of therapy were allowed to continue therapy until disease progression or unacceptable toxicity.

Drug administration was isovolumetric, and amount of CSF equivalent to the volume of drug to be administered was removed before drug administration. Following intralumbar injection, patients were in a supine posture (either flat or Trendelenburg position) for 30 minutes. Following intraventricular administration of the drug, the reservoir was flushed slowly for 1 to 2 minutes with 2 mL of either CSF (removed before drug injection) or preservative-free 0.9% saline and pumped four to six times.

Dose escalation schedule. The starting dose of Spartaject Busulfan was 5 mg for children ≥3 years of age. Children between 2 to 3 years of age received 80% of this dose, based on their lower CSF volume (14). Dose escalation proceeded according to the modified continuous reassessment method as described below. No intrapatient dose escalation was allowed. Subsequent doses were 7.5, 10, 13, 17, and 21 mg (Table 1).

Modified continual reassessment method. The modified continual reassessment method (CRM), as described by Goodman et al., was implemented to estimate the MTD (15). The CRM-estimated MTD is defined as the dose at which 20% of patients are expected to experience dose-limiting toxicity (DLT). The dose-finding MTD is the prespecified dose level closest to the CRM-estimated MTD. The lowest dose level was assigned to the two patients who were first enrolled in the study. Subsequent dose levels were determined to be the level closest to the CRM-estimated MTD without skipping a level that had been assigned to fewer than two patients and were recalculated after the toxicity experience was known for each patient. In the absence of new toxicity information, at most three patients were assigned to the current level. A one-variable logistic function was used to estimate the probability of toxicity at each of the six dose levels. The prior distribution of toxicity for these six dose levels was assumed to be 0.05, 0.10, 0.20, 0.35, 0.50, and 0.70, respectively. A minimum of 18 patients were to be studied and the study would continue until at least six patients have been assigned the recommended MTD and observed for toxicity.

Duration of therapy. Patients were allowed to come off study following 2 weeks of treatment at the discretion of the attending physician. However, any patient who showed decrease in size of the tumor, stable disease, and/or disappearance of malignant cells from the CSF after the 2-week period of drug treatment (course 1) could continue treatment at the same dose once a week for two consecutive weeks (course 2), once a week every other week for two treatments (course 3), and then one treatment per month (course 4 and beyond) thereafter until there was evidence of progressive disease or unacceptable toxicity.

Concurrent therapy. Patients could not receive other anticancer therapy during the first 2 weeks of treatment. Thereafter, patients could be treated with systemic chemotherapy with the exception of agents that were able to significantly penetrate the CSF, including methotrexate (doses over 1 g/m²), thiopeta, high-dose cytarabine, 5-fluorouracil, i.v. 6-mercaptopurine, nitrosoureas, or topotecan. In addition, agents that could cause serious unpredictable central nervous system side effects were prohibited. Other general supportive care was provided as clinically indicated including appropriate antibiotics, steroid therapy, and blood product support.

<table>
<thead>
<tr>
<th>Type of toxicity</th>
<th>No. patients with grade ≥2 toxicity during course 1</th>
<th>Dose level (mg)</th>
<th>No. patients with grade ≥2 toxicity after course 1</th>
<th>Dose level (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelosuppression</td>
<td>3</td>
<td>5, 13</td>
<td>11</td>
<td>5, 7.5, 10, 13, 17</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>4</td>
<td>5, 10, 13</td>
<td>11</td>
<td>5, 7.5, 10, 13, 17</td>
</tr>
<tr>
<td>Hepatic</td>
<td>0</td>
<td>—</td>
<td>2</td>
<td>13, 17</td>
</tr>
<tr>
<td>Metabolic/laboratory</td>
<td>0</td>
<td>—</td>
<td>3</td>
<td>5, 10, 17</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>0</td>
<td>—</td>
<td>5</td>
<td>7.5, 13, 17</td>
</tr>
<tr>
<td>Pain</td>
<td>7</td>
<td>5, 7.5, 13, 17</td>
<td>2</td>
<td>5, 13</td>
</tr>
<tr>
<td>Neurologic</td>
<td>2</td>
<td>13, 17</td>
<td>6</td>
<td>5, 13</td>
</tr>
<tr>
<td>Infection/febrile neutropenia</td>
<td>0</td>
<td>—</td>
<td>5</td>
<td>10, 13</td>
</tr>
</tbody>
</table>

Fig. 1. Frequency of patients receiving each course of intrathecal Spartaject Busulfan.
Definition of DLT. DLT was defined as any grade ≥3 toxicity or any grade 1 to 2 central nervous system toxicity that was either not reversible or only slowly reversible during the first 2 weeks of treatment. Patients who experienced DLT were allowed to recover and continue treatment at the next lower dose level.

Required clinical and laboratory studies before, during, and end of therapy. Physical and neurologic examination, complete blood count with differential, serum electrolytes, blood urea nitrogen, creatinine, liver function tests, calcium, magnesium, and CSF studies (cell count, protein, and cytology) were obtained immediately before the first and subsequent courses. Standard pre-gadolinium and post-gadolinium magnetic resonance imaging (MRI) sequences of the brain and spine were obtained before beginning therapy and immediately before the second course (3rd week of treatment), fourth course (9th week of treatment), and every 8 weeks thereafter. The MRI studies obtained before therapy and following course 1 were centrally reviewed by the Pediatric Brain Tumor Consortium neuroimaging center for assessment of response. The locations and patterns of disease (linear, nodular, or

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>$C_{max}$ (µg/mL)</th>
<th>Terminal half-life (min)</th>
<th>CSF busulfan clearance (mL/min)</th>
<th>CSF busulfan AUC (min·mg/L)</th>
<th>Plasma busulfan AUC (min·mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>144</td>
<td>204</td>
<td>0.859</td>
<td>5.821</td>
<td>44.93</td>
</tr>
<tr>
<td>5</td>
<td>117</td>
<td>78</td>
<td>0.576</td>
<td>8.680</td>
<td>24.20</td>
</tr>
<tr>
<td>5</td>
<td>102</td>
<td>71</td>
<td>1.486</td>
<td>3.364</td>
<td>28.35</td>
</tr>
<tr>
<td>7.5</td>
<td>269</td>
<td>54</td>
<td>0.436</td>
<td>17.206</td>
<td>86.33</td>
</tr>
<tr>
<td>13</td>
<td>536</td>
<td>71</td>
<td>1.557</td>
<td>8.349</td>
<td>63.37</td>
</tr>
<tr>
<td>17</td>
<td>202</td>
<td>73</td>
<td>0.927</td>
<td>18.332</td>
<td>84.29</td>
</tr>
</tbody>
</table>

Abbreviations: $C_{max}$, maximum drug concentration; AUC, area under the concentration-time curve.

Fig. 2. Spartaject Busulfan CSF concentration versus time following administration of drug into Ommaya reservoir at different dose levels in six patients with leptomeningeal disease (A), CSF clearance of intrathecal Spartaject Busulfan versus dose (B), CSF area under the concentration-time curve (AUC) of Spartaject Busulfan versus dose (C). CSF area under the concentration-time curve versus plasma area under the concentration-time curve of Spartaject Busulfan (D).
combined) were determined. Linear disease was measured based on the maximum thickness of the lesion. Nodular disease was assessed based on number of nodules present, and the size of the biggest nodule was measured in two dimensions. The total number of sites involved with disease was determined for each response category.

Assessment of response. Response was assessed based on MRI scan of brain and spine and results of CSF cytology. Irradiated lesions in patients who received focal irradiation to the brain or spine within 1 week before study entry were not used in the assessment of response. Complete response was defined as complete disappearance on MRI of all enhancing tumor and mass effect on a stable or decreasing dose of corticosteroids. For patients with positive CSF cytology before treatment, two consecutive ventricular and/or lumbar CSF had to be negative for tumor cells. Partial response was defined as ≥50% reduction in size of bulky leptomeningeal tumor by bidimensional measurement on MRI, on a stable or decreasing dose of corticosteroids. For patients with initially positive CSF cytology, two consecutive ventricular and/or lumbar CSF samples had to be negative. Progressive disease was defined as >25% increase in the bidimensional measurement of bulky leptomeningeal disease on MRI or conversion of a previously negative CSF cytology to positive. Although the “sugar-coated” appearance of leptomeningeal disease is difficult to quantify, new areas of contrast enhancement in the brain or spinal cord were considered to be evidence of progressive disease. Stable disease was defined as failing to fulfill the criteria for a complete response, partial response, or progressive disease.

Pharmacokinetic studies. Cerebrospinal fluid and plasma were obtained for Busulfan pharmacokinetics only in patients with Ommaya reservoirs. Samples were obtained before and at 15, 30 minutes, 1, 2, 3, and 5 hours after administration of the first dose of study drug via the Ommaya reservoir and lumbar route, respectively. Busulfan concentrations were determined by gas chromatography, as previously described (16). The lower limit for sensitivity of this assay was 0.04 μg/mL. The standard curve was linear from 0.05 to 2 μg/mL. Ventricular CSF busulfan concentrations found in samples obtained following administration via an Ommaya reservoir were found to be substantially elevated compared with CSF collected after lumbar administration or plasma samples and were diluted with drug-free plasma for assessment within the standard concentration range (16). Variability in the assay was 2.5% to 5.1% (coefficient of variation). Concentration-time data sets were evaluated by both noncompartmental and compartmental techniques using a standard, two-stage approach with WinNonlin software (Pharsight, Inc., Mountain View, CA).

Results

Patient characteristics. A total of 28 patients were enrolled in this study. Twenty-four patients received all four intrathecal treatments, but only 23 of them were evaluable for assessment of DLT. These patients were treated at the following dose levels: 5 mg (n = 7 patients), 7.5 mg (n = 2), 10 mg (n = 3), 13 mg (n = 7), and 17 mg (n = 4). Patient characteristics are listed in Table 2. These 23 patients received a total of 144 doses of intrathecal Spartaject Busulfan with a median of four doses per patient (range, 4-19). The median number of courses received was 2 (range, 1-14; Fig. 1).

DLT. Twenty-three patients were evaluable for assessment of toxicity. Of the remaining five patients, three did not receive all four doses during the first course of treatment, one did not receive any treatment, and one was inequivalent because the platelet count fell below the minimum value required for eligibility between registration and initiation of treatment. DLT occurred in three patients (Table 1). One patient developed grade 3 emesis at 5 mg, one patient developed a grade 3 headache (n = 1) at 17 mg, and another patient enrolled at the same dose level experienced grade 3 arachnoiditis (n = 1). The seven patients treated with 13 mg of intrathecal Spartaject Busulfan did not experience any significant toxicity attributable to the study drug. The CRM-estimated MTD was 14.4 mg; hence, the dose-finding recommended dose for subsequent phase II trials of this agent in children with leptomeningeal disease is 13 mg.

Other toxicities. Other toxicities regardless of attribution are listed in Table 3. Because patients with bulky parenchymal or systemic tumor were allowed to receive systemic chemotherapy following the first 2 weeks of intrathecal chemotherapy, it was generally felt that the adverse events were related to the systemic chemotherapy rather than the intrathecal Spartaject Busulfan. Similarly, the reported neurologic events, which are briefly summarized below, were in most instances attributable to the patients’ underlying leptomeningeal disease. Two patients were reported to have peripheral neuropathy and pain in the setting of disease progression, one nearly 5 months after completion of the intrathecal Spartaject Busulfan, and the other while also receiving a multiagent chemotherapy regimen that included thalidomide, a well-known cause of peripheral neuropathy. Although tumor progression could account for most of these neuropathic symptoms, intrathecal Spartaject Busulfan could not totally be excluded as a contributing factor to the neuropathy. Another patient had the sudden onset of headache and emesis 2 hours following the seventh dose of intrathecal Spartaject Busulfan and was subsequently placed on life support. MRI scan of brain revealed extensive leptomeningeal disease with diffuse cortical ischemia, and the patient died following withdrawal of life support. A limited postmortem examination of the brain revealed diffuse leptomeningeal disease without evidence of drug-induced toxic inflammation, and the cause of death was attributed to progressive leptomeningeal disease.

Responses after the first course of treatment. Twenty-three patients completed the first 2 weeks of therapy and were evaluable for response. Nine patients had stable disease, and 14 patients had progressive disease after the first course of intrathecal Spartaject Busulfan.

Pharmacokinetic studies. Pharmacokinetic data was available for six patients enrolled on this trial (Table 4). Busulfan CSF concentrations rapidly declined after drug administration in a biexponential manner for most patients with a median terminal half-life of 74.5 minutes (range, 54-204 minutes; Table 4; Fig. 2A). There was no evidence for dose-dependent changes in busulfan terminal half-life, area under the curve, or clearance in the CSF in the limited number of patients for whom data is available (Table 4; Fig. 2A-D). Ventricular busulfan concentrations were very high (>100 μg/mL) following Ommaya reservoir administration at the MTD; however, lumbar delivery of the drug resulted in ventricular CSF concentrations that were several logs lower (data not shown). In addition, low but measurable concentrations of busulfan were observed in concurrently collected plasma samples. The maximal plasma concentrations (0.15-0.38 μg/mL) were observed between 30 minutes and 2 hours following injection. There seemed to be a direct association between ventricular CSF and plasma busulfan exposure (Fig. 2D).

Discussion

Busulfan, a dimethanesulfonyloxyalkane, is effective following oral administration in patients with chronic myeloid leukemia or in the setting of bone marrow transplantation for
a wide variety of hematologic and solid tumor malignancies, including tumors of the central nervous system (9, 10, 17). Aaron et al. showed that the noncrystalline form of busulfan has antitumor activity against a panel of tumor cell lines derived from childhood high-grade glioma, adult high-grade glioma, ependymoma, and medulloblastoma, including a panel of four medulloblastoma cell lines with laboratory-generated or clinically acquired resistance to 4-hydroperoxycyclophosphamide and melphalan (9). Busulfan has also shown activity against a panel of s.c. and i.c. tumor xenografts derived from childhood high-grade glioma and ependymoma (9, 10).

Because the conventional form of busulfan is not water-soluble and hence unsuitable for intrathecal use, the microcrystalline water-soluble formulation, Spartaject busulfan, was evaluated for preclinical toxicity and efficacy study in a nude rat model (12). This study showed significant increases in median survival (123-142%) compared with a PBS control (P < 0.001) following treatment with either single or multiple doses of intrathecal Spartaject Busulfan and showed no evidence of tumor growth at autopsy or on serial histologic sections of brain and spinal cord. Preclinical pharmacokinetic studies were done in two healthy nonhuman primates at a dose of 0.5 mg (equivalent to 5 mg in humans) of Spartaject Busulfan either given via the intraventricular (through a catheter placed in the IV ventricle) or lumbar route. When administered via the intralumbar route, the ventricular CSF concentration was initially low (0.2 μmol/L) but increased to 8 μmol/L (2 μg/mL) at 1.5 hours following injection. Following intraventricular administration, the maximum drug concentration in the lumbar CSF was 5 μmol/L (1.25 μg/mL) at 45 minutes. The drug was also well tolerated in these animals.

Based on the above preclinical studies, an adult phase I study of intrathecal Spartaject Busulfan was initiated in patients with refractory leptomeningeal disease at Duke University Medical Center, Durham, NC (13). A preliminary report indicated that 21 adult patients with leptomeningeal disease have received doses ranging from 2.5 to 17 mg via the intraventricular route only through an Ommaya reservoir (patients with ventriculoperitoneal shunts were excluded from this study). Objective responses were noted in two patients with breast carcinoma and one patient with malignant glioma, and three additional patients have had stable disease following treatment. In a further follow-up, an additional 23 patients have been treated in this trial at doses of 21, 27, 34, and 41.5 mg via the intraventricular route without DLT.

The starting dose for our pediatric phase I study was one dose level below the dose safely tolerated by adults, which was 5 mg at the time of initiation of the pediatric study. Patients were treated via the Ommaya reservoir and lumbar routes to obtain even drug exposure throughout the neuraxis. In contrast to the adult trial described above, DLT after intrathecal Spartaject Busulfan were observed in children with leptomeningeal disease at a significantly lower dose of 17 mg and included headache, neck pain, and chemical arachnoiditis. These side effects are typically seen following intrathecal administration of chemotherapeutic agents (5, 6, 18, 19). The reasons for lower tolerance of intrathecal Spartaject Busulfan in children compared with adults are unclear. It is possible that patients with spinal

leptomeningeal disease have a lower volume and slower rate of flow of CSF in this area. Thus, treatment via the lumbar route, as in this study, might have resulted in prolonged exposure of arachnoid membranes and nerve roots to a higher concentration of drug and a consequent increase in neurotoxicity.

Administration of intrathecal Spartaject Busulfan via an Ommaya reservoir resulted in very high ventricular CSF drug concentrations. These values were several-fold above those observed in the plasma following myeloablative doses of the drug in the setting of bone marrow transplant (20). Maximal ventricular concentrations ranged from ~100 to 500 μg/mL and are far above the reported IC50 concentration of 0.25 to 1 μg/mL achieved in vitro cytotoxicity assays for this agent (21). On the other hand, in contrast to what was observed in the nonhuman primate, ventricular CSF concentrations of drug were extremely low in two patients following treatment via the lumbar route, possibly related to poor CSF distribution caused by leptomeningeal disease. This finding also supports the strategy of alternating the route administration of drug between the Ommaya reservoir and lumbar puncture.

In conclusion, intrathecal Spartaject Busulfan was well tolerated by children with refractory or recurrent leptomeningeal disease. The MTD of intrathecal Spartaject Busulfan defined in this trial was 13 mg and should be the dose used in future phase II trials of this drug in children with leptomeningeal disease.

Appendix A. Pediatric Brain Tumor Consortium

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