Feasibility of Four Consecutive High-Dose Chemotherapy Cycles With Stem-Cell Rescue for Patients With Newly Diagnosed Medulloblastoma or Supratentorial Primitive Neuroectodermal Tumor After Craniospinal Radiotherapy: Results of a Collaborative Study

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Purpose: **This study was designed to determine the feasibility and safety of delivering four consecutive cycles of high-dose cyclophosphamide, cisplatin, and vincristine, each followed by stem-cell rescue, every 4 weeks, after completion of risk-adapted craniospinal irradiation to children with newly diagnosed medulloblastoma or supratentorial primitive neuroectodermal tumor (PNET).**

Patients and Methods: **Fifty-three patients, 19 with high-risk disease and 34 with average-risk disease, were enrolled onto this study. After surgical resection, high-risk patients were treated with topotecan in a 6-week phase II window followed by craniospinal radiation therapy and four cycles of high-dose cyclophosphamide (4,000 mg/m² per cycle), with cisplatin (75 mg/m² per cycle), and vincristine (two 1.5-mg/m² doses per cycle). Support with peripheral blood stem cells or bone marrow and with granulocyte colony-stimulating factor was administered after each cycle of high-dose chemotherapy. Treatment of average-risk patients consisted of surgical resection and craniospinal irradiation, followed by the same chemotherapy given to patients with high-risk disease. The expected duration of the chemotherapy was 16 weeks, with a cumulative cyclophosphamide dose of 16,000 mg/m² and a planned dose-intensity of 1,000 mg/m²/wk.**

Results: **Fifty of the 53 patients commenced high-dose chemotherapy, and 49 patients completed all four cycles. The median length of chemotherapy cycles one through four was 28, 27, 29, and 28 days, respectively. Engraftment occurred at a median of 14 to 15 days after infusion of stem cells or autologous bone marrow. The intended dose-intensity of cyclophosphamide was 1,000 mg/m²/wk; the median delivered dose-intensity was 1,014, 1,023, 974, and 991 mg/m²/wk for cycles 1 through 4, respectively; associated median relative dose-intensity was 101%, 102%, 97%, and 99%. No deaths were attributable to the toxic effects of high-dose chemotherapy. Early outcome analysis indicates a 2-year progression-free survival of 93.6% ± 4.7% for the average-risk patients. For the high-risk patients, the 2-year progression-free survival is 73.7% ± 10.5% from the start of therapy and 84.2% ± 8.6% from the start of radiation therapy.**

Conclusion: **Administering four consecutive cycles of high-dose chemotherapy with stem-cell support after surgical resection and craniospinal irradiation is feasible in newly diagnosed patients with medulloblastoma/supratentorial PNET with aggressive supportive care. The early outcome results of this approach are very encouraging.**

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HIGH-DOSE CHEMOTHERAPY with bone marrow or stem-cell rescue has been used as an adjuvant to primary therapy or as salvage therapy to treat adult[1-9] and pediatric[10-14] patients with various primary or relapsed malignancies, including relapsed tumors of the CNS.[15-20] In children with brain tumors, high-dose chemotherapy has been used most often in patients with high-grade glioma before irradiation[21] or at the time of disease progression[22-24] or to avoid radiotherapy for infants and very young children.[25,26]

Treatment for patients with newly diagnosed medulloblastoma or primitive neuroectodermal tumor (PNET) includes surgical resection followed by craniospinal radiotherapy. Adjuvant chemotherapy has been shown to increase the cure rate for patients with high-risk or average-risk disease and is now a standard part of contemporary management.[27]

Amongst the agents effective in these embryonal CNS tumors, cyclophosphamide has proven activity against relapsed medulloblastoma and PNET at conventional doses in chemotherapy-naive patients or at high doses in heavily pretreated patients.[28,29]

Cyclophosphamide has a steep dose-response curve[30,31] supporting the assumption that increasing the administered dose should increase tumor-cell kill.[32,33] Prolonged myelo-

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suppression has limited the opportunities to escalate dosage of cyclophosphamide. However, with recent advances in hematopoietic stem-cell apheresis and rescue with peripheral blood stem cells or autologous marrow and the availability of hematopoietic cytokines to enhance marrow recovery, high doses of cyclophosphamide are now tolerated with myelosuppression of minimal duration. Thus, the dose-intensity can be optimized, as repeated dosing is now possible in shorter periods of time.[34,35]

Multiple cycles of high-dose chemotherapy with stem-cell rescue have been used to treat a number of malignant tumors including lung cancer in adults and brain tumors in children.[36-39] However, no study has demonstrated the feasibility of sequential delivery of multiple courses of high-dose chemotherapy to patients with newly diagnosed medulloblastoma/supratentorial PNET immediately after extensive irradiation of the craniospinal axis, which includes approximately 40% of the total marrow space.

In this report, we document the feasibility of using high-dose cyclophosphamide combined with cisplatin and vincristine with stem-cell rescue and hematopoietic cytokine support and provide early outcome data in children with newly diagnosed medulloblastoma or supratentorial PNET after surgical resection and craniospinal irradiation.

PATIENTS AND METHODS

Eligibility

Between October 1996 and June 1999, 53 patients with previously untreated medulloblastoma or supratentorial PNET were treated at one of the participating institutions (Baylor College of Medicine, Houston, TX, n = 8; Royal Children's Hospital, Melbourne, Australia, n = 9; The Children's Hospital at Westmead, Sydney, Australia, n = 4; and St Jude Children's Research Hospital, Memphis, TN, n = 32). The clinical characteristics of these patients at the time of diagnosis are listed in Table 1.

Patients aged ≥ 3 and ≤ 21 years old at the time of diagnosis and who had not previously received chemotherapy or irradiation were eligible for enrollment onto the protocol. Prior corticosteroid therapy was allowed. Patients had to begin treatment within 28 days of definitive surgery. Additional eligibility criteria included normal renal function (serum creatinine ≤ 1.2 mg/dL or technetium clearance ≥ 70 mL/min · m^2]), normal liver function (AST ≤ 1.5 times normal and bilirubin ≤ 1.5 mg/dL), normal bone marrow function (hemoglobin ≥ 10 g/dL, WBC count ≥ 3,000/μL, absolute neutrophil count [ANC] ≥1,500/μL, and platelets ≥ 100,000/mm^3) and an the Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 3, except in cases of posterior fossa syndrome. The institutional review board of each participating institution approved the protocol, and informed consent for treatment was obtained from patients, parents, or legal guardians, as appropriate.

Disease was staged as high risk or average risk using postsurgical tumor volume and a modification of the Chang staging system.[40] Average-risk disease was defined as (1) absence of metastatic disease as confirmed by gadolinium-enhanced magnetic resonance imaging (MRI) of the head and spine and by the absence of tumor cells in the cytologic examination of lumbar CSF at least 10 days after surgical resection of the tumor; (2) absence of bony metastasis as confirmed by bone scan; (3) gross total resection or ≤ 1.5 cm^2 residual disease as confirmed by documentation in the operative note and by gadolinium-enhanced postoperative MRI of the head no more than 48 hours after surgery. Patients with brainstem invasion documented in the operative note but with no visible tumor on MRI were considered to have average-risk disease.

Table 1. Patient Characteristics

		No. of Patients
Sex		
Male		33
Female		20
Age, years		
Median	6.9	
Range	3.1-17.1	
Average-risk disease		34
High-risk disease		19
M staging		
M0		38
M1		3
M2		2
M3		10

High-risk disease was defined as (1) presence of metastatic disease documented by gadolinium-enhanced MRI of the head and spine or by the presence of malignant cells in the lumbar spinal fluid, confirmed by cytologic examination obtained at least 10 days after surgery; and (2) presence of more than 1.5 cm^2 residual disease as confirmed by postoperative gadolinium-enhanced MRI. Patients with metastatic disease outside the neuraxis were not eligible for protocol treatment.

Treatment Regimen

All patients underwent an attempt at maximal surgical resection of the tumor. Patients with high-risk disease were treated with a 6-week phase II window of topotecan therapy. After completing the window therapy, the patients underwent repeat imaging studies to assess the response of the tumor to topotecan. High-risk patients next received craniospinal irradiation (36 Gy, M0-1; 39.6 Gy, M2-3) and three-dimensional conformal boost to the tumor bed (total dose, 55.8 Gy) and, where appropriate, local sites of metastasis (total dose, 50.4 Gy). The median duration of radiation therapy was 1.5 months. After a 6-week rest period, patients began four cycles of high-dose chemotherapy, each followed by stem-cell or bone marrow rescue (Table 2).

After surgical resection, patients with average-risk disease began craniospinal irradiation (23.4 Gy), followed by three-dimensional conformal boost to the posterior fossa (cumulative dose, 36 Gy) and the tumor bed (total, 55.8 Gy). The median duration of irradiation was 1.4 months. After a 6-week rest period, they received the same schedule of high-dose chemotherapy as those with high-risk disease (Table 2).

Twenty-four hours after the completion of each cycle of chemotherapy, all patients received peripheral blood stem cells (PBSCs), bone marrow, or both. All patients received daily support with granulocyte colony-stimulating factor (G-CSF) until the ANC was ≥ 2,000/μL for 2 consecutive days. The planned duration of each cycle was 28 days; the next cycle of chemotherapy was to begin once the hemoglobin

Table 2. Treatment Plan for Each Cycle of Chemotherapy

Day	Chemotherapy
−4	Cisplatin 75 mg/m^2 IV; vincristine 1.5 mg/m^2 (max 2 mg) IV
−3	Cyclophosphamide (2 g/m^2) IV; mesna by continuous infusion
−2	Cyclophosphamide (2 g/m^2) IV; mesna by continuous infusion
−1	Postchemotherapy hydration
0	Infusion of PBSCs or bone marrow
+1	G-CSF 5 μg/kg/d SC/IV till ANC $>$ 2,000/μL for 2 consecutive days after expected nadir
+6	Vincristine 1.5 mg/m^2 (max 2 mg) IV

Abbreviations: IV, intravenously; SC, subcutaneously.

concentration was $\geq$ 8 g/dL, the platelet count was $\geq$ 75,000/μL, and the ANC was $\geq$ 1,500/μL.

Stem-Cell Collections

In most cases, PBSCs were harvested and cryopreserved after mobilization with G-CSF before radiation therapy (for patients with average-risk disease) or after topotecan administration (for patients with high-risk disease). Patients in whom mobilization could not be accomplished before starting craniospinal irradiation underwent a bone marrow harvest before starting chemotherapy. Of the 49 patients who received all four cycles of chemotherapy, PBSCs were harvested from 28 patients, bone marrow was harvested from 11, and both PBSCs and bone marrow were harvested from 10 (Table 3).

Supportive Care

After placement of double-lumen Hickman line, patients were admitted to the hospital for each course of high-dose chemotherapy. Mesna and continuous hydration were given with cyclophosphamide to prevent hemorrhagic cystitis. All patients received trimethoprim-sulfamethoxazole as prophylaxis against *Pneumocystis carinii* pneumonia. If patients could not tolerate trimethoprim-sulfamethoxazole, they were treated with either dapsone or aerosolized pentamidine according to the preference of the investigator. Transfusions of platelets were administered as necessary to maintain a platelet count greater than 30,000/mm^3, and transfusions of irradiated packed RBCs were administered to maintain a hematocrit concentration of greater than 20% to 25%. If patients experienced fever (body temperature of $\geq$ 38°C) and had an ANC $<$ 500/μL, they were hospitalized and treated with broad-spectrum antibiotics. In addition, any patient with a $>$ 10% weight loss from the time of starting therapy received nutritional support using total parenteral nutrition (TPN), nasogastric feeding tube, or both.

Table 3. Stem-Cell Harvest

	Average No. of CD34$^+$ Cells Collected (cells/kg)	Average No. of Nucleated Cells Collected (cells/kg)
PBSCs (n = 28)		
Median	15.2×10^6	–
Range	6×10^6 -1.6×10^9	
BM (n = 11)		
Median	–	6.0×10^8
Range		3×10^8-1.1×10^{11}
PBSCs + BM (n = 10)		
Median	7.1×10^6	4.0×10^8
Range	2.9×10^6 -2.67×10^7	0.92×10^8-1.88×10^9

Patient Monitoring

During protocol therapy, the disease status of all patients and the types of toxicity they experienced were monitored with appropriate laboratory assessments and imaging studies. Version 2 of National Cancer Institute Common Toxicity Criteria was used to grade toxicity. After completion of therapy, all patients were observed on a regular basis to monitor physical and disease status as well as their neuroendocrine and neuropsychologic function.

Statistical Considerations

Though not the primary end point of the study, delivered dose-intensity of cyclophosphamide was defined as the total amount of drug given in milligrams per square meter over the number of weeks cyclophosphamide was administered. Relative dose-intensity was the ratio of the delivered dose-intensity to the expected dose-intensity (1,000 mg/m^2/wk). Descriptive statistics were used to report the effects of variables of interest on the feasibility of delivering high-dose chemotherapy.

For both the average-risk and high-risk groups, progression-free survival (PFS) was measured from the date of enrollment onto the study to the date of progression, death, or last contact. In addition, PFS was measured from the date of radiation therapy, after the topotecan window, to the date of progression, death, or last contact in the high-risk subset. The method of Kaplan and Meier[41] was used to estimate PFS distributions. Standard errors of the Kaplan-Meier estimates were calculated by the method of Peto et al.[42]

RESULTS

Feasibility of Chemotherapy Delivery

Of the 53 patients with newly diagnosed medulloblastoma or PNET who were enrolled during the study period, 50 received high-dose chemotherapy per protocol. Two of the three patients who did not receive such therapy had experienced disease progression after completion of radiation therapy, and were treated with alternative therapy; the third case did not meet the ECOG criteria for high-dose chemotherapy. Of the 50 patients who received high-dose chemotherapy, 49 completed all four cycles (Fig 1). The planned time to completion of high-dose chemotherapy was 16 weeks, and the median time to completion was 16.9 weeks in the 49 patients (range, 15.4 to 23.3 weeks). The planned duration of each cycle of high-dose chemotherapy was 28 days, and the median duration of chemotherapy cycles 1, 2, 3, and 4 were 28, 27, 29, and 28 days, respectively (range for all cycles, 24 to 60 days) (Table 4). The intended dose-intensity of cyclophosphamide was 1,000 mg/m^2/wk. The median delivered dose-intensity was 1,014, 1,023, 974, and 991 mg/m^2/wk for cycles 1 through 4, respectively; associated median relative dose-intensity was 101%, 102%, 97%, and 99% (Table 5).

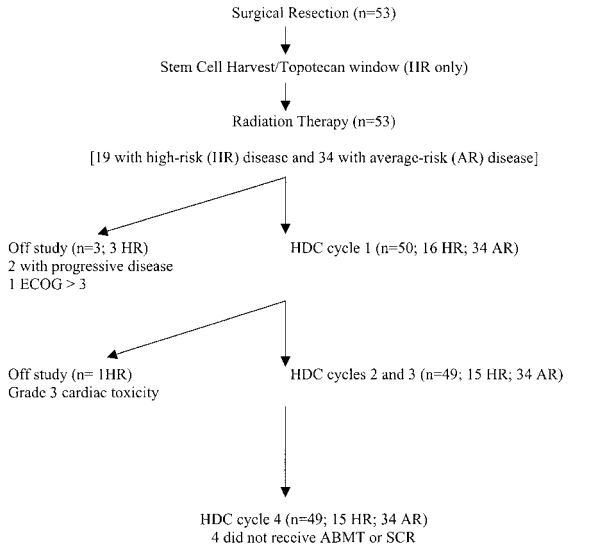

Fig 1. Progression of patients through chemotherapy regimen.

Seven patients required reduction of cyclophosphamide dosage throughout the course of treatment. Because of delayed hematopoietic recovery during the third cycle, one patient did not receive high-dose cyclophosphamide during the final cycle. Two patients experienced reduced pulmonary function after the first and third cycles: one received a half dose of cyclophosphamide for the second cycle but was able to resume planned chemotherapy for the remainder of the cycles, and the other received a 25% reduction during the fourth cycle. Pulmonary function returned to normal after completion of therapy for both these patients. For another patient, the cyclophosphamide dose was reduced by 25% for both days of the final cycle because of absence of stem cells for rescue. Because of delayed hematopoietic recovery during the third cycle, one patient did not receive high-dose cyclophosphamide during the final cycle. One child experienced grade 3 fever without infection on the day she was to receive the second daily dose of cyclophosphamide during the third cycle; this finding prevented the delivery of that dose. For another patient, the second cycle of cyclophosphamide was modified downward by 50% because of prolonged fever and neutropenia during the first cycle of chemotherapy. He tolerated the second course well and received the regular dose of cyclophosphamide for the remaining two cycles. Finally, one patient did not receive the second dose of cyclophosphamide during one cycle because of an abnormal ECG reading that was later found to have been because of a technical problem. The patient received subsequent courses of cyclophosphamide at the appropriate doses and on schedule. In five patients, the cyclophosphamide dose was determined on the basis of the body-surface area at the time of the first round of chemotherapy. No adjustments were made for weight loss during chemotherapy. This resulted in five patients receiving a total of 10 cycles of chemotherapy with doses of cyclophosphamide ranging from 5% to 21% higher than the planned dose (median, 8%).

Renal function tests and audiography were performed before every cycle of chemotherapy to determine the dose and toxicity of cisplatin. The results of these tests led to modifications of the cisplatin dosage for 15 patients by the fourth cycle of chemotherapy. In nine patients, the cisplatin dose was reduced by 50% because of grade 3 ototoxicity. One patient was legally blind; hence, cisplatin was electively discontinued after two cycles of high-dose chemotherapy to ensure preservation of hearing. In four patients, the dose of cisplatin was reduced because of renal toxicity, including temporary renal failure in one patient, who did not get reduced dose of cisplatin because of pre-existing renal toxicity. In all four patients, renal toxicity resolved after completion of therapy. In one patient, the cisplatin dose was reduced because of parent request.

Table 4. Length of Cycle and of WBC Recovery Time With G-CSF Support

	Cycle 1		Cycle 2		Cycle 3		Cycle 4	
	No.	%	No.	%	No.	%	No.	%
Length of cycle, days								
Median	28		27		29		28	
Range	26-49		25-47		26-56		24-60	
Patients with length of cycle > 31 days								
Total	15	30	12	24	17	35	15	31
Average-risk disease	8	24	8	24	14	41	12	35
High-risk disease	7	44	4	27	3	20	3	20
Days on G-CSF until ANC > 2,000/μL								
Median	15		14		15		14	
Range	9-23		9-27		8-27		8-22	

Table 5. Delivered Dose-Intensity of Cyclophosphamide

	Cycle 1	Cycle 2	Cycle 3	Cycle 4
Length of cycle, weeks				
Median	4.0	3.9	4.1	4.0
Range	3.7-7.0	3.6-6.7	3.7-8.0	3.4-8.6
Dose administered, mg/m^2				
Median	4,000	4,100	4,000	4,000
Range	3,600-4,200	2,000-4,500	2,000-4,500	0-4,900
Dose-intensity, mg/m^2/wk				
Median	1,014.0	1,023.2	974.3	990.7
Range	537.5-1,095.5	525.9-1,204.3	455.9-1,178.9	0-1,359.1
Relative dose-intensity, %				
Median	101	102	97	99
Range	54-110	53-120	46-118	0-136

Vincristine doses were modified for 15 patients primarily because of absence of deep tendon reflexes, neuropathic pain, and foot and wrist drop. One patient did not receive the final daily dose of vincristine because of low blood counts. Neurologic toxicity resolved within a year of completion of therapy.

Characteristics of Hematopoietic Toxicity and Engraftment

All patients had neutropenia after each cycle of high-dose chemotherapy; however, only 55% of the cycles resulted in hospital admission for fever and neutropenia. The percentage of patients requiring hospitalization was 62%, 45%, 61%, and 55%, for cycles 1 through 4, indicating that there was no cumulative risk for fever and neutropenia. The median length of stay per cycle ranged from 5 to 7 days (Table 6).

Low platelet counts required transfusion of platelets in 92% of the cycles; most patients required no more than two transfusions per cycle during the first three cycles. However, 57% of the patients required three or more transfusions during the last cycle. Transfusions of RBCs were required during 88% of the cycles; three fourths of these patients required no more than two transfusions per cycle for each of the four cycles (Tables 6 and 7).

The number of PBSCs infused per cycle ranged from 1.0 $\times$ 10^6 to 23.8 $\times$ 10^6 cells/kg for the 131 cycles, and the number of bone marrow cells delivered ranged from 0.54 $\times$ 10^8 to 20 $\times$ 10^8 cells/kg for 75 cycles. With the use of G-CSF and PBSC or bone marrow support, the resulting median engraftment time (until the ANC exceeded 2,000/μL for 2 consecutive days) ranged from 14 to 15 days per cycle, although the time to engraftment was slightly longer during the final two courses for patients who received bone marrow (Table 8). However, there was no clinically significant difference in engraftment characteristics between patients who received stem cells and those who received bone marrow.

Of the 49 patients who completed all four courses of chemotherapy, four did not receive bone marrow or stem-cell rescue after the final cycle of therapy. One did not receive any cyclophosphamide and thus did not require stem-cell support. Three of the four did not have sufficient cells for rescue. One of these three patients received a reduced dose of cyclophosphamide, whereas the other two were given the full dose and required 31 and 33 days, respectively, for recovery of platelet count.

Table 6. Hematologic Toxicity

	Chemotherapy Cycle			
	1	2	3	4
WBC toxicity				
No. of patients per cycle	50	49	49	49
No. of days neutrophil count $\leq$ 500				
Median	14	13	13	13
Range	8-21	8-21	9-25	8-19
No. of patients hospitalized for neutropenia	31	22	30	27
Length of stay for neutropenia, days				
Median	7	5	5	7
Range	2-34	2-17	2-17	2-18
Platelet toxicity				
No. of patients per cycle	50	49	49	49
No. of days of platelet count $\leq$ 20,000				
Median	16	17	16	16
Range	0-29	6-32	6-34	9-36
No. of platelet transfusions per patient				
Median	2	2	2	3
Range	0-6	0-17	0-8	0-12
RBC toxicity				
No. of patients per cycle	50	49	49	49
No. of RBC transfusions per patient				
Median	1	1	2	2
Range	0-6	0-4	0-5	0-6

Table 7. Transfusion Data

	Cycle 1	Cycle 2	Cycle 3	Cycle 4
No. of RBC transfusions				
0	10	7	5	2
1-2	33	30	32	33
3-5	5	12	12	13
> 5	1	0	0	1
No. of platelet transfusions				
0	5	4	2	4
1-2	30	26	24	17
3-5	13	15	19	21
> 5	1	4	4	7

Other Toxicities

Most of the toxicity that occurred during high-dose chemotherapy was anticipated. However, one patient required intervention with digoxin and furosemide because of grade 3 cardiotoxicity (reduced ejection fraction) and hypotension after the first course of high-dose chemotherapy. The patient was subsequently treated off-study with a different chemotherapy regimen and is currently free of disease. There were no instances of hepatic veno-occlusive disease or hemorrhagic cystitis recorded.

Infection

Among the patients who were admitted to the hospital during chemotherapy for fever and neutropenia or suspected sepsis, the etiology was definitely ascertained in only seven patients. Infectious agents included herpes zoster infection (two patients), central line sepsis (two patients), pneumonia (one patient), varicella (one patient), and disseminated aspergillosis (one patient).

Other Complications

One patient who experienced renal failure during the second cycle of therapy also experienced transient elevation of hepatic transaminase activity (grade IV toxicity) during that cycle; changes resolved before the next course of chemotherapy. The patient had no residual hepatic or renal complications noted before death 4 months after chemotherapy because of rapid onset of metastatic disease.

Nausea and vomiting were treated with antiemetics; however, five patients required hospitalization. Abdominal pain and gastritis necessitated at least one hospitalization. Seizures and mucositis required one admission each.

Nutritional Support

Supplementation and nutritional support were necessary for 22 patients. Eighteen patients received TPN for maintenance of adequate weight and protein intake during high-dose chemotherapy. Three patients received nutritional support through a nasogastric tube. One patient received TPN for one cycle but received nasogastric feeding for subsequent cycles. The median duration of TPN was 111 days (range, 2 to 168 days).

PFS

Of the 53 patients enrolled onto the study, five patients have died because of progressive disease. Of the 48 patients alive at last follow-up, the median time at risk is 2.5 years (minimum, 1.3 years; maximum, 4.2 years). The 2-year PFS for the 36 average-risk patients is 93.6% ± 4.7%. Of the 19 high-risk patients, four had progressive disease while on the topotecan window. The 2-year PFS from the start of therapy is 73.7% ± 10.5%. All high-risk patients went on to receive radiation therapy. The 2-year PFS from the start of radiation therapy is 84.2% ± 8.6%.

Table 8. Time to Marrow Recovery for Patients Rescued With PBSC Versus BM

	Days on G-CSF			
	Cycle 1	Cycle 2	Cycle 3	Cycle 4
Patients rescued only with PBSCs*				
Median	14.5	14	14.5	14
Range	9-23	9-24	8-27	8-22
Patients rescued only with bone marrow†				
Median	15	14	16	15.5
Range	11-21	12-27	12-27	10-20

*Dose range of 1.0×10^6 to 23.8×10^6 $CD34^+$ cells/kg.
†Dose range of 0.54×10^8 to 20.0×10^8 cells/kg.

DISCUSSION

The current study demonstrates that an intensive chemotherapy regimen is feasible and safe after surgical resection and craniospinal irradiation in the front-line treatment of pediatric patients with medulloblastoma and supratentorial PNET. Using PBSC or autologous bone marrow rescue and cytokine support, we were able to deliver high doses of chemotherapy within the planned short 28-day interval. Adequate blood cell counts were required before each new cycle of chemotherapy was begun, requiring rapid hematopoietic recovery if the next course of chemotherapy was to be delivered on schedule. Four cycles of cyclophosphamide delivered over a median of 16.9 weeks resulted in an average median dose-intensity of 1,000.55 mg/m^2/wk. Each cycle of high-dose chemotherapy was delivered according to the planned 28-day schedule for approximately two thirds of the patients.

Our study is the first to test delivery of multicyclic, dose-intensive chemotherapy over a relatively short period of time as front-line management of pediatric medulloblastoma or supratentorial PNET immediately after postoperative craniospinal irradiation. The now standard CDDP/CCNU/vincristine regimen published by Packer et al[43] uses

Table 9. Comparison of Cyclophosphamide Dose-Intensity

	Cumulative Dose (mg/m^2)	Planned Dose-Intensity ($mg/m^2/wk$)
A 9961	16,000	333
POG 9031	16,000	500
CCG 9931	9,000	600
SJMB96	16,000	1000

eight cycles of chemotherapy planned over a 48-week period after completion of radiation therapy. A contemporary national protocol incorporating cyclophosphamide instead of CCNU includes multiple cycles of standard-dose cyclophosphamide. The Pediatric Oncology Group (POG) 9031 protocol delivered the same cumulative dose as our study (16,000 mg/m^2) but at half the dose-intensity (500 $mg/m^2/wk$).[44] Other protocols do not approach the cumulative dose or the dose-intensity of this study (Table 9). This study delivers cyclophosphamide not only at high doses but also within a short period of time; thus, in theory this treatment regimen optimizes the efficacy of this agent.

Because of their toxicity profiles, most high-dose chemotherapy regimens used to treat pediatric CNS tumors have been associated with mortality rates ranging from 2% to 16%; to date, we note no toxic deaths in the current trial. Furthermore, veno-occlusive disease, a common hepatic toxicity seen in 4% to 15% of patients with similar high-dose chemotherapy regimens for pediatric brain tumors, was not seen in this patient population.[15-17,25]

The dose-limiting toxicity of cyclophosphamide is myelosuppression; however, the hematologic toxicity is significantly attenuated with cytokine support and stem-cell and/or bone marrow rescue. Two thirds of our patients required one to two transfusions of packed RBCs and platelets between cycles. Fifty percent required three or more platelet transfusions in the later cycles. In addition, although approximately half of the patients were hospitalized for fever and neutropenia during each cycle, the length of stay for most was 1 week or less. The planned dose-intensity for the study was well tolerated, especially in view of the temporal proximity to craniospinal irradiation; the high dose-intensity was achieved because of the ameliorated myelosuppression associated with hematopoietic rescue.

Previous studies have shown that cyclophosphamide doses delivered in this study carry a slight risk of hemorrhagic pericarditis, a toxicity that we did not encounter in our study.[31] Nonhematologic toxicity has been uncommon to date; patients were monitored closely for cardiac and pulmonary complications, using echocardiograms and pulmonary function tests. When renal function was compromised or ototoxicity occurred, the dose of cisplatin was reduced. Ototoxicity was the most common nonhematologic toxicity in this patient population and is a well-documented toxicity related to the cumulative effects of cisplatin and radiotherapy.[45,46] In addition, neurosensory and neuromotor function were closely monitored to detect toxicity that might require an adjustment in the dose of vincristine. Except for the hearing deficits, toxicities associated with vincristine and cisplatin resolved shortly after completion of therapy.

Even though the outcome results of our study are preliminary, they compare very favorably with those in the published literature. For average-risk patients treated with similarly reduced-dose radiation therapy and conventional chemotherapy, a recently completed study documented a 3-year PFS at 86% $\pm$ 4%.[43] The POG 9031 study was designed for high-risk patients. The study compared the 2-year event-free survival of children with newly diagnosed high-risk medulloblastoma randomized to receive chemotherapy before irradiation versus chemotherapy after radiation for patients with metastatic disease at presentation. The 2-year event-free survival was 61% $\pm$ 6.8% in the former group versus 74% $\pm$ 6.5% in the latter.[44]

High-dose chemotherapy with stem-cell rescue is used to treat various CNS and other pediatric malignancies that are associated with a relatively poor prognosis. Multiple short cycles of tandem high-dose chemotherapy optimizes dose-intensity. This strategy of dose optimization has shown promise in treating patients with high-risk neuroblastoma, soft tissue sarcoma, and non-Hodgkin's lymphoma.[5,9,11] Rapid delivery is possible because of autologous stem-cell or bone marrow rescue, which overcomes the myelosuppression caused by the treatment regimen. We have demonstrated that this high-dose, multicyclic therapy is feasible and safe in the postirradiation setting; further follow-up is needed before definitive conclusions can be made regarding outcome in comparison with conventional treatment regimens.

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