High Incidence of Veno-Occlusive Disease With Myeloablative Chemotherapy Following Craniospinal Irradiation in Children With Newly Diagnosed High-Risk CNS Embryonal Tumors: A Report From the Children's Oncology Group (CCG-99702)

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Background. The outcomes with high-risk central nervous system (CNS) embryonal tumors remain relatively poor despite aggressive treatment. The purposes of this study using postirradiation myeloablative chemotherapy with autologous hematopoietic stem cell rescue (ASCR) were to document feasibility and describe toxicities of the regimen, establish the appropriate dose of thiotepa, and estimate the overall survival (OS) and event-free survival (EFS). ***Procedure.*** The Children's Cancer Group conducted this pilot study in children and adolescents with CNS embryonal tumors. The treatment consisted of induction chemotherapy to mobilize hematopoietic stem cells, chemoradiotherapy, and myeloablative consolidation chemotherapy with ASCR. ***Results.*** The study accrued 25 subjects in 40 months and was closed early due to toxicity, namely, veno-occlusive disease (VOD) of the liver, more recently termed sinusoidal obstructive syndrome (SOS). Of 24 eligible subjects, three of 11 (27%) receiving thiotepa Dose Level 1 (150 mg/m^2/day × 3 days) and three of 12 (25%) receiving de-escalated Dose Level 0 (100 mg/m^2/day × 3 days) experienced VOD/SOS. One additional subject experienced toxic death attributed to septic shock; postmortem examination revealed clinically undiagnosed VOD/SOS. The 2-year EFS and OS were 54 ± 10% and 71 ± 9%, respectively. The 5-year EFS and OS were 46 ± 11% and 50 ± 11%. ***Conclusions.*** The treatment regimen was deemed to have an unacceptable rate of VOD/SOS. There was complete recovery in all six cases. The overall therapeutic strategy using a regimen less likely to cause VOD/SOS may merit further evaluation for the highest risk patients. Pediatr Blood Cancer 0000;00:000–000. © 2016 Wiley Periodicals, Inc.

Key words: CCG-99702; high-risk medulloblastoma (MB); myeloablative chemotherapy; primitive neuroectodermal tumor (PNET); sinusoidal obstructive syndrome (SOS); veno-occlusive disease (VOD)

INTRODUCTION

Medulloblastoma (MB) is the most common malignant brain tumor in children.[1] Patients have historically been risk stratified according to age, presence of metastases, extent of resection, and more recently, degree of anaplasia.[2–4] Standard- or average-risk patients, defined by these criteria, have experienced improved survival over the past three decades with combined chemotherapy and radiotherapy, leading to a 5-year survival of greater than 75%.[5] However, the outcomes for central nervous system (CNS) primitive neuroectodermal tumors (PNETs) and high-risk MB remain relatively poor despite aggressive treatment strategies using surgery, radiotherapy, and chemotherapy. Five-year survival for these high-risk patients has historically been reported between 30% and 70%.[5–11] Molecular subgroups of MB have since been elucidated,[12–15] and molecular risk stratification is now being incorporated into clinical trial design.[16,17] Still, more effective regimens must be developed for certain subgroups of patients that carry the worst

Abbreviations: ANC, absolute neutrophil count; ASCR, autologous hematopoietic stem cell rescue; AT/RT, atypical teratoid rhabdoid tumor; CCG, Children's Cancer Group; CNS, central nervous system; CSF, cerebrospinal fluid; DLT, dose-limiting toxicity; EFS, event-free survival; IRS, Intergroup Rhabdomyosarcoma Study; MB, medulloblastoma; MRI, magnetic resonance imaging; OS, overall survival; PBSC, peripheral blood stem cell; PNET, primitive neuroectodermal tumor; SOS, sinusoidal obstructive syndrome; VOD, veno-occlusive disease

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prognoses. Such regimens may include maximally aggressive chemotherapy approaches and the addition of molecularly targeted agents.

With the highest risk groups of patients in mind, we report the results of the Children's Cancer Group pilot study (CCG-99702) consisting of induction chemotherapy primarily aimed at mobilizing hematopoietic stem cells to facilitate sufficient collection, chemoradiotherapy, and postirradiation myeloablative consolidation chemotherapy supported by autologous hematopoietic stem cell rescue (ASCR) for children and adolescents with high-risk CNS embryonal tumors, largely PNET and MB. This study was initially conceived based on promising preliminary results using high-dose chemotherapy in recurrent MB,[18,19] and was one of two pilot trials conducted concurrently by the CCG designed as potential experimental arms in a subsequent randomized Phase III study in this population. The results of this study are important to consider as future clinical trials are being designed for patients with high-risk embryonal tumors.

METHODS

Patient Eligibility

Eligible subjects were at least 3 and less than 22 years of age at the time of diagnosis of a high-risk embryonal tumor. The target tumors for this study included "high-risk" MB (M_{1-3} or M_0 with >1.5 cm^2 residual), supratentorial PNET (M_{0-3}), and atypical teratoid rhabdoid (AT/RT) tumors (M_{0-3}). Patients with M_4 disease (extraneural metastasis) were not eligible. Central pathology and neuroradiology review were not performed. Protocol therapy was required to start within 31 days of original surgery. Additional criteria to proceed with consolidation included adequate peripheral blood stem cell (PBSC) collection during induction, defined as $>15 \times 10^6$ CD34$^+$ cells/kg harvested. Institutional review board approval was required at each participating institution. All study participants (or their parent/guardian) provided informed consent.

Study Design and Treatment Plan

The primary aims of this study were (1) to document the feasibility and describe the toxicities of this regimen using myeloablative chemotherapy with ASCR in this population, (2) demonstrate the safety of delaying radiotherapy by approximately 1 month to facilitate PBSC collection, and (3) establish the appropriate dose of thiotepa using a limited dose-escalation design. The secondary aim was to estimate the event-free survival (EFS) and overall survival (OS) of patients with high-risk embryonal tumors treated with postirradiation myeloablative chemotherapy and ASCR. The treatment plan details are summarized in Table I.

Induction began within 31 days of initial surgery and included one course of chemotherapy to induce PBSC mobilization and allow sufficient collection to support subsequent consolidation therapy. The treatment of residual or metastatic tumor and clinically inapparent systemic disease was also a goal of induction chemotherapy. Hematopoietic stem cells were harvested from peripheral blood when the CD34 count was $>20 \times 10^3/\mu$l. One or more harvesting apheresis sessions were performed until at least 5×10^6 CD34$^+$ cells/kg were available for each of the three planned reinfusions in consolidation therapy (total collection 15×10^6 CD34$^+$ cells/kg).

Chemoradiotherapy started once PBSC harvest was complete and the absolute neutrophil count (ANC) was $\geq 1{,}000/\mu$l and platelet count was $\geq 100{,}000/\mu$l within 28 days of starting induction. Weekly vincristine for a total of eight doses started the same week in which radiotherapy was initiated. Irradiation of the craniospinal axis followed by a boost to the primary tumor and any CNS metastatic sites was delivered. The target volume for the boost was the whole posterior fossa if the primary site was in the infratentorial region. The boost target volume for supratentorial tumors and metastatic tumors was 1 cm around the tumor as seen on the presurgical magnetic resonance imaging (MRI) scan. Upon completion of radiotherapy, subjects had a 4- to 6-week rest period.

Consolidation therapy consisted of three courses of chemotherapy, each supported by ASCR. Course 1 was initiated within 4–6 weeks of completion of radiotherapy when the ANC was $\geq 1{,}000/\mu$l and platelet count was $\geq 75{,}000/\mu$l. Subsequent courses were started on Day 21 of the prior course or when ANC was $\geq 750/\mu$l and platelet count was $\geq 30{,}000/\mu$l without filgrastim for at least 24 hr. Courses 1 and 3 (consolidation A) were identical myeloablative regimens containing thiotepa. The starting dose level was 150 mg/m^2/day $\times$ 3 days and the de-escalation dose used was 100 mg/m^2/day $\times$ 3 days. Individual subjects received the same dose level of thiotepa for Courses 1 and 3 unless a dose reduction was required due to toxicity. PBSC were infused on Day 7 and filgrastim was started on the same day. Consolidation B was administered during Course 2. PBSC were infused on Day 5, and filgrastim was started on the same day.

Subject Evaluations

Pretreatment evaluation included MRI of brain and spine, lumbar cerebrospinal fluid (CSF) cytological evaluation, complete blood count, renal function, audiometric evaluation, and bone marrow evaluation. MRI of brain (and MRI of spine and lumbar CSF, if previously abnormal) was repeated prior to initiation of chemoradiotherapy and consolidation and upon completion of therapy. Renal function was evaluated prior to each course of consolidation. Audiometric evaluation was repeated at the end of Course 2 and upon completion of therapy. Veno-occlusive disease (VOD)/ sinusoidal obstructive syndrome (SOS) was defined as "the presence of at least two of the following: total bilirubin >2 mg/dl, weight gain $>20\%$, liver enlargement, and right-upper quadrant pain in the absence of another cause."

The extent of tumor resection was based primarily on postsurgical MRI in addition to neurosurgeon's assessment of residual tumor. Recurrence was defined as reappearance of tumor in any site in subjects who had previously responded completely to therapy. Progressive disease was defined in subjects with previously detectable residual disease as an increase of $>25\%$ in tumor area, compared to immediate prestudy area or area of best prior response at that site, or the reappearance of tumor in sites of involvement that had responded completely to therapy (including surgery), or the appearance of new tumor in previously uninvolved sites.

TABLE I. Treatment Plan

Day	Therapy
Induction	
0	Cyclophosphamide 2.1 g/m^2 with MESNA 420 mg/m^2 i.v.
	Vincristine 1.5 mg/m^2 i.v. (maximum dose 2 mg)
1	Cyclophosphamide 2.1 g/m^2 with MESNA 420 mg/m^2 i.v.
	MESNA 420 mg/m^2 i.v. infused over 3 hr and repeated as a 15-min i.v. bolus at hours 6, 9, 12
2+	Start filgrastim 10 μg/kg/day s.c. at least 1 day after completion of chemotherapy (continue for minimum of 7 days and until ANC $\geq$ 10,000/μl)
	One or more harvesting apheresis sessions until total 15 $\times$ 10^6 CD34$^+$ cells/kg were available
Chemoradiotherapy	
5 days/week	Irradiation of the craniospinal axis to 36 Gy followed by
	boost of 19.8 Gy to primary tumor and CNS metastatic sites (180 cGy daily doses)
Weekly	Vincristine 1.5 mg/m^2 i.v. (maximum dose 2 mg) every 7 days for a total of eight doses
	4–6 weeks rest period upon completion of radiotherapy
Consolidation (three courses)	
Courses 1 and 3 (consolidation A)	
0	Carboplatin 500 mg/m^2/day (or AUC = 7 mg/mL/min) i.v.
	Vincristine 1.5 mg/m^2 i.v. (maximum dose 2 mg)
1	Carboplatin 500 mg/m^2/day (or AUC = 7 mg/mL/min) i.v.
2	Thiotepa per dose level assignment
3	Thiotepa per dose level assignment
4	Thiotepa per dose level assignment
5	–
6	–
7	PBSC infusion; start filgrastim 5 μg/kg/day s.c. (continue for minimum of 7 days and until ANC $\geq$ 10,000/μl)
Course 2 (consolidation B)	
0	Carboplatin 500 mg/m^2/day (or AUC = 7 mg/mL/min) i.v.
	Vincristine 1.5 mg/m^2 i.v. (maximum dose 2 mg)
1	Carboplatin 500 mg/m^2/day (or AUC = 7 mg/mL/min) i.v.
2	Cyclophosphamide 2.1 g/m^2 with MESNA 420 mg/m^2 i.v.
3	Cyclophosphamide 2.1 g/m^2 with MESNA 420 mg/m^2 i.v.
4	–
5	PBSC infusion; start filgrastim 10 μg/kg/day s.c. (continue for minimum of 7 days and until ANC $\geq$ 10,000/μl)

ANC, absolute neutrophil count; AUC, area under the curve; CNS, central nervous system; i.v., intravenously; PBSC, peripheral blood stem cell; s.c., subcutaneously.

Statistical Considerations

The initial sample size calculation was based on the dose-escalation design for thiotepa in consolidation. The study required at least 48 subjects to select a dose level.

The dose escalation algorithm was designed to select the highest thiotepa dose level associated with $<$10% levels of thiotepa-related dose-limiting toxicity (DLT). A dose level at which $\geq$3 of 12 subjects experienced DLT was considered toxic. The definition of DLT associated with thiotepa included toxic death, VOD/SOS, hemolytic uremic syndrome, septic shock, failure to recover counts, as well as any grade 3 or grade 4 toxicity not resolving to grade 2 within 7 days.

Delays in the start of radiation therapy were monitored continually. Delays of greater than 2 weeks (i.e., past Day 35 of induction), if occurring in more than 10% of subjects, was considered unacceptable. A Bayesian monitoring rule with prior density Beta (1,6.6) on the probability P of delay past Day 35 was a planned trigger for examination of the causes.

The endpoints for treatment efficacy were EFS and OS. EFS was defined as the time between diagnosis and progression, recurrence of disease, occurrence of a second malignant neoplasm, or death by any cause. OS was defined as the time between diagnosis and death by any cause. Subjects who did not experience an event for EFS or OS were censored at their last follow-up date. Data collection cut-off was March 30, 2007. EFS and OS distributions were estimated using the product limit (Kaplan–Meier) method with standard error performed via the Peto–Pike formula, which updates standard error upon censoring. Survival distributions among subgroups were compared using the log-rank test.

RESULTS

Subject Selection

Twenty-five subjects were accrued over a 40-month period from July 1999 to November 2002. One subject who had no residual tumor was declared ineligible when the original designation of CSF involvement (M1) was changed to negative (M0) on re-review of cytology. Of the 24 eligible subjects, 11 were assigned to thiotepa Dose Level 1 (150 mg/m^2/day), 12 were

TABLE II. Summary of Clinical Characteristics

Subject	Age at Dx (y)	Tumor histology	Tumor location	Extent of resection	M-stage	Thiotepa (mg/m^2/d)	VOD/ SOS	Death	Last F/U from Dx (y)	Off-therapy reason
1	11	PNET	Cerebrum	PR	M0	150	No	Yes	0.5	Death (progression)
2	14	PNET	Brain, NOS	Bx	M3b	150	Yes	No	6.5	Completed protocol
3	7	MB[a]	Cerebellum	NTR	M3b	150	No	Yes	1.1	Completed protocol
4	4	MB	Cerebellum	NTR	M0	150	No	No	5.9	Completed protocol
5	5	MB[a]	Cerebellum	STR	Unknown	150	No	No	6.4	Completed protocol
6	15	PNET[b]	Cerebrum	NTR	M0	150	No	No	6.9	Relapse/progression
7	6	AT/RT	Brain, NOS	GTR	M0	150	Yes	Yes	1.8	Withdrawn
8	18	PNET	Occipital	NTR	Unknown	150	No	Yes	1.4	Completed protocol
9	4	MB	Cerebellum	NTR	M3b	150	No	Yes	3.8	Completed protocol
10	7	PNET	Frontal	GTR	M0	150	No	No	4.7	Completed protocol
11	3	MB	Cerebellum	STR	M3a	150	Yes	Yes	0.5	Toxicity
12	15	PNET	Cerebrum	GTR	M3a	100	No	No	6.6	Completed protocol
13	16	PNET	Spinal cord	NTR	M3a	100	No	No	5.9	Completed protocol
14	8	PNET	Brainstem	NTR	M2	100	No	Yes	2.6	Completed protocol
15	4	PNET	Ventricle	GTR	M0	100	No	No	6.7	Completed protocol
16	5	AT/RT	Parietal	NTR	M3b	100	No	Yes	0.9	Completed protocol
17	8	MB	Cerebellum	NTR	M3a	100	No	Yes	2.8	Completed protocol
18	4	MB	Cerebellum	NTR	M1	100	No	No	4.9	Completed protocol
19	10	Pineo	Brain, NOS	PR	M0	None	No	No	4.3	Withdrawn
20	5	Pineo	Brain, NOS	STR	M0	100	No	No	5.3	Completed protocol
21	11	MB	Cerebellum	GTR	M3b	100	Yes	No	5.2	Toxicity
22	15	MB	Cerebellum	NTR	M3b	100	Yes	Yes	0.5	Death (sepsis)
23	6	MB[c]	Brainstem	GTR	M2	100	Yes	Yes	2.9	Toxicity
24	4	PNET	Parietal	GTR	M0	100	Yes	Yes	3.7	Completed protocol

[a]PNET histology defined during study period, designated medulloblastoma due to cerebellar location; [b]medullomyoblastoma, designated PNET due to supratentorial location; [c]medulloblastoma histology defined during study period, final designation remains medulloblastoma despite reported brainstem location due to specific documentation of desmoplastic variant (characteristic of medulloblastoma). Protocol definitions for metastatic stage (M-stage): no evidence of subarachnoid or hematogenous metastasis (M0), microscopic tumor cells found in cerebrospinal fluid (M1), gross nodular seeding demonstrated in the intracranial subarachnoid space or ventricular system distant from primary site (M2), gross nodular seeding in the spinal subarachnoid space without evidence of intracranial seeding ($M3_a$), and gross nodular seeding in the spinal subarachnoid space as well as intracranial seeding ($M3_b$). AT/RT, atypical teratoid/rhabdoid tumor; Bx, biopsy; d, day; Dx, diagnosis; F/U, follow-up; GTR, gross total resection; MB, medulloblastoma; NOS, not otherwise specified; NTR, near total resection; Pineo, pineoblastoma; PNET, primitive neuroectodermal tumor; SOS, sinusoidal obstructive syndrome; STR, subtotal resection; VOD, veno-occlusive disease; y, years.

assigned to de-escalated Dose Level 0 (100 mg/m^2/day), and one was not assigned a dose level due to a protocol deviation during induction.

Demographics and Baseline Characteristics

The median age at diagnosis of the 24 eligible patients was 7.3 years (range: 3.1–18.4 years). Sixteen (66.7%) were male and 18 (75%) were Caucasian. Nine (37.5%) had non-metastatic (M0) tumors, 12 (50%) had PNET (one with histologic diagnosis of medullomyoblastoma, designated as PNET in data analysis due to supratentorial location), eight (33.3%) had MB (one of which was designated desmoplastic MB), two had AT/RT, and two had pineoblastoma (included with PNET in survival analysis). Eighteen subjects (75%) underwent at least near total resection of the primary tumor. Key characteristics, treatment details, and outcomes for each subject are summarized in Table II.

PBSC Collection Prior to Radiotherapy and Initiation of Consolidation Therapy Following Chemoradiotherapy

All subjects began radiotherapy by Day 38 (range 18–38 days, median 26 days). No relapse or progression occurred during induction. Therefore, up-front collection of hematopoietic stem cells did not cause delay in initiation of radiotherapy and was deemed feasible. One subject discontinued protocol therapy before starting consolidation by parental/patient choice. The remaining 23 subjects had adequate PBSC harvested and started consolidation therapy with adequate hematopoietic function within 4–6 weeks of completing chemoradiotherapy.

Toxicity

The most frequent severe toxicity was dose-limiting VOD/SOS during consolidation. Three of 11 (27%) subjects on thiotepa Dose Level 1 and 3 of 12 (25%) subjects on de-escalated Dose Level 0 experienced VOD/SOS. The onset of this toxicity was not limited to any specific course number. Four of six with VOD/SOS (two from each dose level) relapsed at 2, 6, 16, and 18 months. Further details of dose-limiting VOD/SOS are summarized in Table III. While the protocol definition of DLT due to VOD/SOS was met in six cases, it is noted that only three required supportive care in the hospital setting (including one requiring intensive care). There was complete recovery of VOD/SOS in all cases.

One additional subject experienced toxic death attributed to septic shock. Postmortem examination revealed VOD/SOS

TABLE III. Summary of Dose-Limiting VOD/SOS in Consolidation

Subject	Thiotepa dose level (mg/m^2/day)	Course	Peak total bilirubin (mg/dl)	Portal venous flow on ultrasound	Level of care required	Outcome
2	150	3	10.6	Normal flow	Minimal (no hospitalization) ursodiol given	VOD/SOS resolved; alive without disease
7	150	2	33.5	Flow reversed	Prolonged hospitalization (no intensive care): oxygen, paracentesis, thoracentesis, diuretics, defibrotide	VOD/SOS resolved; death due to progressive disease
11	150	1	12	Flow reversed	Intensive care: one vasopressor, ventilator, repeated paracentesis	VOD/SOS resolved; death due to progressive disease
21	100	2	10.7	Flow reversed	Prolonged hospitalization (no intensive care): diuretics given	VOD/SOS resolved; alive without disease
22	100	3	6.8	Not assessed	Intensive care: three vasopressors, antibiotics, ventilator then oscillator, white cell infusions, plasma exchange	Death attributed to septic shock; VOD/SOS noted at time of autopsy
23	100	2	6.3	Normal flow	Minimal (no hospitalization)	VOD/SOS resolved; death due to progressive disease
24	100	3	2.2	No reversal of flow: "Variability of portal vein slightly abnormal"	Minimal (no hospitalization)	VOD/SOS resolved; death due to progressive disease

SOS, sinusoidal obstructive syndrome; VOD, veno-occlusive disease.

that had not been clinically recognized. This subject was a 15-year-old female with metastatic MB who had started consolidation course 3. Prior to administration of the final dose of thiotepa, she developed hypotension, fever, hematuria, and shaking chills. She stabilized after 6 days in intensive care and received autologous PBSC infusion. Two days later, she was transferred back to intensive care with anasarca, hematuria, hematochezia, and hematemesis. Abdominal CT showed typhlitis, cystitis, and cholecystitis. The subject experienced progressive multisystem organ failure and died after discontinuation of ventilator support. Autopsy examination revealed pulmonary hemorrhage, hemorrhage in the trachea and stomach, hemorrhagic cystitis, and anasarca. Though preliminary results suggested recurrent tumor in the posterior fossa, the final autopsy report did not confirm recurrent disease. This subject was also found to have VOD/SOS on autopsy (therefore included in Table III), which was thought to possibly play a role in her death, though this toxic death was technically attributed to septic shock.

Other toxicities were not dose-limiting or were expected. Consolidation therapy at both dose levels resulted in grade 4 neutropenia and thrombocytopenia for most subjects. One subject on Dose Level 0 experienced grade 3 diarrhea with hypotension due to *Clostridium difficile* colitis during consolidation. Fluid resuscitation and inotropic support with dopamine were required. Of note, at least three long-term survivors are known to have persistent, apparently permanent, and complete alopecia. No secondary malignancies have been reported. No grade 3 or 4 ototoxicity was reported during chemoradiotherapy or consolidation.

EFS and OS

There were 12 deaths, with 11 due to tumor progression and one due to septic shock. The 2-year EFS and OS were $54 \pm 10\%$ and $71 \pm 9\%$, respectively. The 5-year EFS and OS were $46 \pm 11\%$ and $50 \pm 11\%$. Neither the EFS distribution (Fig. 1A) nor the OS distribution (Fig. 1B) was significantly different for subjects with PNET (including pineoblastoma) compared to those with MB (log-rank *P*-values are 0.58 and 0.28, respectively). EFS and OS were not significantly different between the two dose levels studied (log-rank *P*-values are 0.34 and 0.71, respectively, at 5 years).

DISCUSSION

In this pilot study, the treatment regimen was deemed to have an unacceptably high rate of VOD/SOS as defined in the protocol. There was complete recovery in all six cases, only three requiring hospitalization for supportive care. Still, this regimen is no longer used in practice.

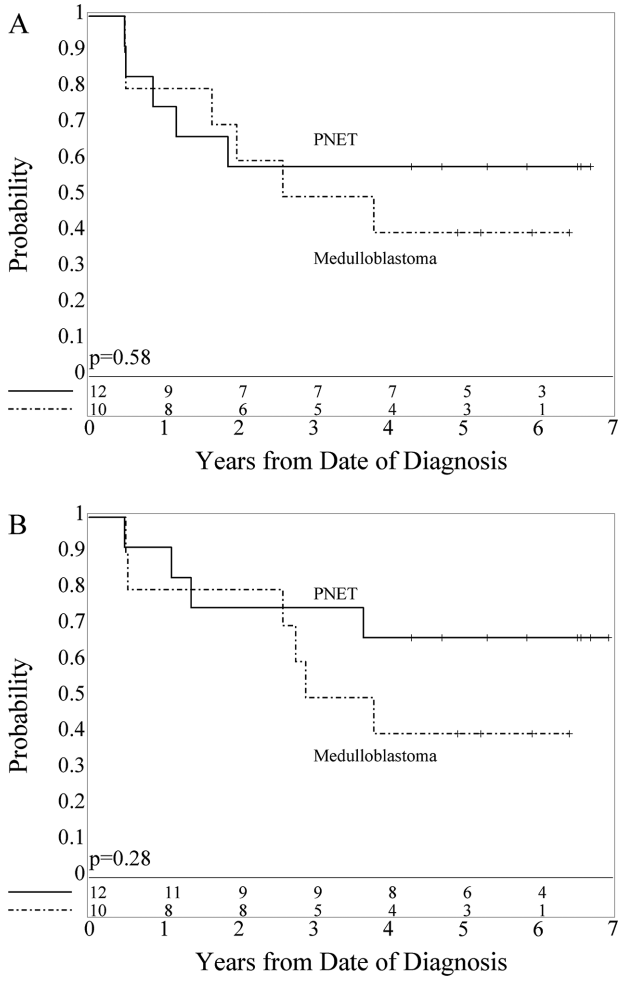

Fig. 1. (**A**) Event-free survival (EFS) for primitive neuroectodermal tumor (PNET) including pineoblastoma (5-year EFS 58 ± 15%) and high-risk medulloblastoma (5-year EFS 40 ± 15%); (**B**) overall survival (OS) for PNET including pineoblastoma (5-year OS 67 ± 15%) and high-risk MB (5-year OS 40 ± 16%).

CCG-99702 demonstrated that delivering an up-front course of chemotherapy to mobilize and collect hematopoietic stem cells did not cause delay in initiation of radiotherapy and was feasible. The OS and EFS associated with this regimen suggests that the overall therapeutic strategy using a regimen less likely to produce VOD/SOS may merit further evaluation in the design of future trials for patients with PNET. The general strategy may be relevant for MB patients with high risk for relapse based on increasing molecular insight.

High-dose chemotherapy with ASCR showed early promise in patients with recurrent MB.[18,19] Given that prior reports showed little chance of long-term survival for patients with recurrent MB,[20] these results supported the evaluation of high-dose chemotherapy with ASCR in newly diagnosed high-risk MB patients as designed in CCG-99702. A decade later, the efficacy and role of high-dose chemotherapy in the recurrent setting was questioned. A large collective experience of this treatment approach was summarized by Gajjar and Pizer following an international consensus and state of the art workshop held in Milan in 2006.[21] From the eight studies represented in this comprehensive review of outcomes, the authors concluded that a very limited number of previously irradiated patients were successfully treated following relapse of MB/PNET using a strategy based on high-dose chemotherapy. The discrepancy in outcomes appeared to be at least in part explained by the superior outcomes reported with thiotepa-based myeloablative regimens compared with nonthiotepa-based regimens, especially for patients with disseminated MB at recurrence.[22,23] It is also now recognized that additional radiotherapy may be associated with better treatment outcomes at relapse,[22,24] which was likely a confounding factor in several prior reports about the efficacy of high-dose chemotherapy.

VOD/SOS is characterized histologically by marked sinusoidal fibrosis, necrosis of pericentral hepatocytes, and narrowing and fibrosis of central veins with diffuse damage to the centrilobular zone of the liver.[25] Clinically, it is a form of toxic liver injury that leads to tender hepatomegaly, fluid retention, and hyperbilirubinemia following cytotoxic therapy.[26,27] The incidence of VOD/SOS in the stem cell transplant population varies, depending on differences in conditioning regimens.[26–31] Our regimen included thiotepa and carboplatin during courses 1 and 3 of consolidation, and cyclophosphamide and carboplatin during course 2 of consolidation. Thiotepa has been implicated in chemotherapy regimens causing VOD/SOS,[32] and cyclophosphamide-based conditioning regimens have been implicated in the allogeneic stem cell transplant literature.[25,26] Based on *in vitro* studies, cyclophosphamide is thought to be one of the most important hepatic toxins among drugs used in conditioning regimens.[33–36] Individual variability in drug metabolism is also felt to be a major contributor for developing VOD/SOS following cyclophosphamide-based regimens.[37] The Intergroup Rhabdomyosarcoma Study (IRS) group reported an unexpected complication of VOD in children treated on IRS IV compared to prior IRS studies and suggested that escalation of the cyclophosphamide dose to 2.2 g/m^2 (with vincristine and actinomycin doses and schedule unchanged) triggered the development of VOD/SOS.[38]

The liver toxicity we saw following administration of myeloablative chemotherapy may have also been enhanced by the recent completion of craniospinal irradiation. Transplant regimens using cyclophosphamide and total-body irradiation >13.2 Gy may cause VOD/SOS in 50% of cases.[26] In an analysis of Wilms tumor patients treated according to the SIOP-9 protocol (actinomycin and vincristine ± other agents and ± radiotherapy according to surgical stage and histology), 64 of 511 participants developed VOD. Radiotherapy was a significant risk factor ($P < 0.001$).[39] Our patient population received 36 Gy to the craniospinal axis. The medial segment of the left lobe of the liver would be expected to receive scatter dose via the anterior exit beam. Though the dose to this focal segment is presumably closer to 12 Gy, it is possible that this contributed to liver toxicity on this regimen. As proton beam radiotherapy becomes a more common treatment modality, such scatter dose may be less of a factor.

Thiotepa-containing high-dose chemotherapy regimens have been tolerated in recurrent disease settings, though they are typically administered many months to years after up-front therapy including radiotherapy.[18,40,41] VOD/SOS is reported

very rarely in the Head Start regimens for newly diagnosed patients, despite cumulative doses of 900 mg/m^2 of thiotepa and 10.5 g/m^2 of cyclophosphamide.[42–45] However, this population is not irradiated prior to receiving this therapy. The St. Jude group has treated newly diagnosed high-risk MB patients with four cycles of cyclophosphamide-based, high-dose chemotherapy (in combination with cisplatin and vincristine) with ASCR following 36 Gy craniospinal irradiation and reported no cases of VOD/SOS.[10] Notably, there is no vincristine administered during radiotherapy on the St. Jude protocols compared to 8 weekly doses administered during chemoradiotherapy on the regimen we report here. VOD/SOS associated with Wilms tumor and rhabdomyosarcoma treatment has been reported with vincristine and actinomycin alone.[39,46,47] Though the VOD/SOS is often attributed to actinomycin, it is possible that vincristine plays a role in this treatment complication.[46]

We therefore suspect that the use of thiotepa following craniospinal irradiation with extended weekly vincristine led to the high incidence of VOD/SOS on this study. The short duration of rest between craniospinal irradiation and initiation of myeloablative chemotherapy may have also played a role. The St. Jude regimen prescribes a rest period of at least 6 weeks following completion of radiotherapy, while our regimen had a rest period between 4 and 6 weeks after radiotherapy completion and even shorter rest period after completion of weekly vincristine.

As future clinical trials are designed for patients with high-risk embryonal tumors, regimens involving postirradiation myeloablative chemotherapy may benefit from extension of the rest period following radiotherapy to a minimum of 6 weeks, limitation or exclusion of weekly vincristine during radiotherapy, and/or placement of standard cytotoxic cycles between radiotherapy and myeloablative consolidation therapy. Additionally, increasing the interval between consolidation cycles from 21 to 28 days to allow more complete organ function recovery may improve the tolerability. Doppler ultrasound surveillance in addition to clinical monitoring could be a useful adjunct for early detection of VOD/SOS,[48] and the recent U.S. Food and Drug Administration approval of defibrotide for the treatment of severe VOD may change the overall risk associated with this toxicity.

In addition to the limitation of a lack of central pathology review, the molecular distinctions between histologic disease entities and their molecular subgroups were not known at the time of CCG-99702 study conception and design. With enrollment of a variety of histologic entities and unknown subgroup status, the survival outcomes of this study are difficult to interpret in the molecular era. For the past few decades, MB patients have been stratified into two distinct risk categories—"standard/average risk" and "high risk"—based primarily on clinical findings at presentation. PNET patients have generally been considered high risk by histology alone and have been included in high-risk MB protocols despite their molecular distinction from MB. Newer clinical trials must stratify using better informed criteria, adding molecular signatures to clinical and histological features, in order to understand the potential benefit of the treatment approach being evaluated. Recently defined very high risk groups, such as MB with *MYC* enrichment and sonic hedgehog MB with *TP53* mutations,[15,49] can be predicted to perform poorly with today's most intensive therapies. Moreover, three molecular subgroups of PNET have been characterized and likely require different therapeutic approaches.[50] The patients with the highest risk embryonal tumors will need new strategies to achieve better outcomes, for example, adding targeted agents to craniospinal radiotherapy and standard cytotoxic and/or myeloablative chemotherapy.

In conclusion, the therapy prescribed on CCG-99702 caused dose-limiting VOD/SOS leading to early closure of the study due to safety concerns. Of note, there was complete resolution in all cases. The up-front mobilization and collection of hematopoietic stem cells did not cause delay in initiation of radiotherapy. The overall strategy using postradiotherapy myeloablative chemotherapy supported by ASCR remains feasible for the highest risk populations.

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