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Pilot Study of Intensive Chemotherapy with Peripheral Hematopoietic Cell Support for Children Less than 3 Years of Age with Malignant Brain Tumors, The CCG-99703 Phase I/II Study. A Report from the Children's Oncology Group

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Abstract

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Background—The primary goals of the CCG-99703 study were to assess the feasibility and tolerability of, as well as the response rate to, a novel dose-intensive chemotherapy regimen.

Methods—Between March 1998 and October 2004, 92 eligible patients were enrolled. Following biopsy/resection, patients received three identical cycles of Induction chemotherapy (vincristine, cyclophosphamide, etoposide and cisplatin) administered every 21–28 days. Patients without tumor progression then received three Consolidation cycles of marrow-ablative chemotherapy (thiotepa and carboplatin) followed by autologous hematopoietic cell rescue.

Results—The Maximum Tolerated Dose (MTD) of thiotepa was 10mg/kg/day x 2 days per cycle. The toxic mortality rate was zero during Induction and 2.6% during Consolidation. Centrally evaluated response rates to Induction and Consolidation in evaluable patients with residual tumor were 73.3% and 66.7% respectively. Disease progression rates on Induction and Consolidation were 4%. Five-year EFS and OS were 43.9±5.2% and 63.6±5% respectively. Gross total resection (GTR) *versus* <GTR were the only significant outcome comparisons: 5-year EFS and OS of 54.4±7% *versus* 28.9±7% (p= .0065) and 75.9±8% *versus* 48.7±8% (p= .0034) respectively. The 5-year EFS for localized (M0) *versus* metastatic (M1+) medulloblastoma was 67.5+/-9.5% *versus* 30+/-14.5% (p= .007). The 5-year EFS and OS for desmoplastic medulloblastoma patients *versus* other medulloblastoma were 78.6+/-11% *versus* 50.5+/-12% (p= .038) and 85.7±9.4% *versus* 60.6±11.6% (p= .046) respectively.

Conclusions—This phase I dose-escalation study of marrow-ablative thiotepa regimen determined an MTD that had acceptable toxicity. Overall survival data justify this strategy for current COG studies.

Keywords

Young children; brain tumors; intensive chemotherapy; infant brain tumor; stem-cell support; high-dose chemotherapy; Children's Oncology Group

Introduction

Brain tumors are the most common solid tumor of childhood, with almost 20% occurring in the first 3 years of life¹. The most recent data available from the CBTRUS Registry from 2015² for the 4-year period 2007–2011 estimated 5,412 cases per year of primary central nervous system (CNS) neuroepithelial tumors in the United States among children less than 4 years of age.

Young children with malignant brain tumors traditionally have experienced very poor survival when treated with maximal surgical resection followed by combinations of irradiation and conventional-dose cytotoxic chemotherapy.^{3, 4, 5, 6} This poor overall survival has been compounded by a high rate of treatment-related, often unacceptable, toxicities.^{7, 8, 9}

The disparity between younger and older children and adolescents in prognosis is a result of several factors. Younger children tend to have a higher incidence of dissemination at diagnosis, which is a major predictor of poor survival. Malignant brain tumors of younger children display a more aggressive biological behavior, with more rapid times to recurrence.

Along with the poor prognosis for survival, these young children are at higher risk for development of severe neuropsychological dysfunction and other life-altering side-effects of treatment. Radiotherapy, a standard modality that results in the best chance of long-term survival for older children and adults with malignant brain tumors, is a major cause of this neuropsychological dysfunction, differentially affecting patients in an inverse age-related function; thus the youngest children represent the most vulnerable population.^{7, 8, 9}

The awareness of both the poor prognosis for survival and radiotherapy-induced side-effects resulted in the development in the mid-1980s to early 1990s of clinical trials for the youngest children with malignant brain tumors that attempted to either delay or even avoid cranial irradiation, with the goal of improving both long-term survival as well as reducing the toxicities of treatment.^{3, 10, 11, 12, 13}

Data from the North American “Head Start” I trial, using 5 cycles of intensive Induction chemotherapy followed by Consolidation with a single cycle of marrow-ablative chemotherapy with autologous bone marrow or peripheral blood rescue, without irradiation, indicated some efficacy but with substantial morbidity and even toxic mortality both during the Induction and Consolidation phases of treatment¹¹. These data, in conjunction with the knowledge gained from other trials referenced above, led to the design of the CCG-99703 prospective single-arm trial - a phase I/II pilot study of the feasibility and toxicity of administration of just three Induction cycles of chemotherapy followed by three “mini” marrow-ablative courses of chemotherapy.

The major goals of the CCG-99703 study were (1) to determine, in a phase I design, the maximal tolerated thiopeta dose administered with a fixed dose of carboplatin for 3 cycles, following upon three cycles of intensive standard-dose cyclophosphamide, cisplatin, etoposide and vincristine and (2) the toxicity and feasibility of administering repetitive cycles of marrow-ablative chemotherapy supported by peripheral blood hematopoietic cells in young children with various malignant brain tumors. This study also was designed to assess the feasibility of harvesting peripheral blood hematopoietic cells in young children and safely treating young children with this intense chemotherapy regimen in a multi-center trial. Finally, within the context of a pilot study enrolling many different histologic types of brain tumors, secondary end-points of the study were to evaluate the complete response rate in patients with evaluable tumor, and event-free and overall survival rates.

Materials and Methods

Patient Selection

The Children’s Cancer Group, CCG, (now having merged with The Pediatric Oncology Group (POG) into the Children’s Oncology Group, COG) enrolled patients into the CCG-99703 study between March 1998 and October 2004. The study was designed for young children between six and 36 months of age newly diagnosed with malignant brain or spinal cord tumors. Children with medulloblastoma, other CNS primitive neuroectodermal tumors (PNET), ependymoma, CNS atypical teratoid/rhabdoid tumors (AT/RT) and choroid plexus carcinoma (CPC) were eligible, provided pathological confirmation of the diagnosis was available for central review. Children with radiologic findings consistent with a diffuse

intrinsic pontine glioma (DIPG) without biopsy were also eligible. Patients were ineligible if they had received any prior treatment for the malignant brain tumor other than surgery and corticosteroids. Adequate renal, hepatic and hematopoietic functions and an anticipated life expectancy of greater than eight weeks were required for eligibility.

Patients were required to enroll on study within six weeks of surgery (or in the case of a DIPG within six weeks of the diagnostic CT or MRI). In those children that were too medically unstable to commence treatment within the six-week period, approval for enrollment was at the discretion of the study chair or vice-chair. Although the leukapheresis and processing of autologous hematopoietic cells was required to be done at a CCG-approved Blood and Marrow Transplantation Center, all other therapy could take place at any CCG institution. The child's parent(s) or legally authorized guardian(s) were required to acknowledge informed consent for study participation in writing. Approval for the use of this treatment protocol by the individual institution's Human Rights Committee was also required.

Pre-Study Extent of Disease Evaluation

Evaluation of disease status and sites of tumor involvement required both pre- and post-operative MRI of the brain and spine performed within 72 hours of surgery, along with a cytological examination of the lumbar cerebrospinal fluid (CSF) obtained following surgery. The primary site was defined as the likely site of origin of the tumor. Spinal cord involvement (in the case of a brain tumor) was defined as unequivocal evidence of spinal involvement on spinal MRI. CSF involvement was defined as the presence of tumor cells in the lumbar CSF obtained prior to treatment. Bone scan or bone marrow aspirates were only required if clinically indicated.

The assessment of presence or absence of residual tumor was based primarily on MRI, but the neurosurgeon's assessment of residual tumor from visual inspection was also considered. The extent of tumor resection was categorized as follows: "biopsy" (an open surgical removal or closed, e.g. stereotactic removal of tissue for the purpose of establishing a pathological diagnosis, with tumor removal less than 10% of the total tumor mass), "partial resection" (removal of 10% to 49% of the tumor mass), "subtotal resection" (removal of 50% to 95% of the tumor mass), "radical subtotal resection", also sometimes referred to as a "near total resection" (removal of >95% but less than 100% of the tumor mass) and "gross total resection" (no visible tumor is left at the time of surgery confirmed by postoperative MRI).

Measurement of residual tumor was based on the squared residual area of tumor, computed by first determining the greatest dimensions of residual tissue in the transaxial, anterior-posterior and cephalad-caudad dimensions, and then calculating the product of the largest two dimensions (cm²). Measurements included solid residual tumor or tumor cysts with enhancing walls only. Tumor cysts without enhancement in the wall were not included in the measurement of tumor residual.

Metastatic (M) staging was graded by standard criteria as follows: M0 (no evidence of spread outside the local site), M1 (positive CSF cytology without radiographic evidence of

spread by neuroimaging studies), M2 (intracranial metastasis), M3 (spinal metastasis) or M4 (tumor metastasis outside the neuraxis).

Treatment

The treatment schema is shown below (Figure 1):

Induction Therapy

Induction consisted of 3 cycles of chemotherapy given at 21-day intervals. Each cycle was to begin when the absolute neutrophil count (ANC) exceeded 750/ μ L and the platelet count exceeded 75,000/ μ L; initiation of chemotherapy cycles was deferred until these criteria were met. The Induction therapy was identical to that used in CCG-9921 Regimen A and consisted of: (1) Cisplatin (CDDP): 3.5 mg/kg (given as an intravenous (IV) infusion over 6 hours), with forced mannitol diuresis given before, during and for at least 8 hours after completion of the CDDP infusion. CDDP was to be given on treatment day 0. (2) Vincristine (VCR): 0.05 mg/kg (given IV bolus injection), to be given on treatment days 0, 7 and 14. (3) Cyclophosphamide (CPM): 60 mg/kg (given IV infused over 1 hour) with furosemide 0.5 mg/kg administered IV 1 hour following CPM. In addition, mesna, 13 mg/kg was given with CPM IV over 1 hour followed by 13 mg/kg over 3 hours by continuous infusion. At completion of the 3-hour infusion, another 13 mg/kg of mesna was given over 15 minutes that was repeated after 3 and 6 hours (for a total of five doses of mesna at 13 mg/kg/dose). CPM and mesna were administered on treatment days 1 and 2. (4) Etoposide (VP-16): 2.5 mg/kg (given IV infused over 1 hour). VP-16 was given on treatment days 1 and 2. This treatment regimen is shown below (Figure 2a):

Modifications of subsequent Induction chemotherapy doses for neutropenia or infection were not to be undertaken during the Induction regimen. Dose modifications for CDDP were as follows: full dose if the glomerular filtration rate (GFR) or creatinine clearance (CrCl) were > 100 mL/min/1.73 m², two-thirds dose if the GFR or CrCl was between 50–100 mL/min/1.73 m², and CDDP was to be omitted for a GFR or CrCl of < 50 mL/min/1.73 m². If hearing loss following CDDP was equal to or greater than 20 decibels at 500 – 4000 Hz in either ear, CDDP was to be omitted but no modification of dose was to be made for any hearing loss above 4000 Hz. For vincristine, if a grade III or IV peripheral neuropathy developed, then the dose was to be held until resolution and the vincristine was to be restarted at 50% dose and increased as tolerated. If the total bilirubin was > 1.5 but < 1.9 mg/dL, the dose of vincristine was to be reduced to 0.03 mg/kg, and if the total bilirubin exceeded 1.9 mg/dL, the vincristine was to be held. For CPM, if microscopic or gross hematuria developed then mesna was to be given as a 24 hour continuous infusion with the next cyclophosphamide cycle as follows: mesna 19 mg/kg with cyclophosphamide infusion, then mesna 93 mg/kg in required fluid over 20 hours after completion of the cyclophosphamide infusion.

Peripheral Hematopoietic Cell Harvest

All patients were required to have a double-lumen leukapheresis catheter placed prior to therapy. Twenty-four hours after the completion of CPM administration during Induction, filgastrim (Neupogen, G-CSF) at a dose of 5 mcg/kg/day was to be administered

subcutaneously (SQ). When the ANC exceeded 1000/ μ L following the nadir of the neutrophil counts, the G-CSF was increased to 10 mcg/kg SQ and the harvest was conducted approximately two days later. If adequate hematopoietic cells were collected in the first or second harvest post Induction cycles, the G-CSF was to be given at a dose of 5 mcg/kg/day SQ until a post-nadir ANC > 2000/ μ L was reached.

The goal of leukapheresis was to collect sufficient cells such that 5×10^6 /kg CD34+ cells were available for each of the three planned treatments during the Consolidation cycles (i.e. a total of 15×10^6 /kg CD34+ cells). If 15×10^6 /kg CD34+ cells were not obtained following all three collections, the patient was to be removed from the study.

Consolidation with Marrow-ablative Chemotherapy

Patients were eligible for Consolidation if they completed Induction, achieved a minimum collection of 15×10^6 /kg CD34+ cells, were re-staged with brain and spine MRI studies and lumbar CSF cytology and deemed not to have progressed, and met clinical and laboratory criteria to start Consolidation within six weeks of the last dose of Induction therapy. For those patients that had not recovered from Induction therapy, an additional four weeks was allowed to recover as long as they were completely re-staged and found free of tumor progression immediately before Consolidation.

Consolidation therapy included carboplatin and thiotepa. The carboplatin dose was 17 mg/kg IV infusion over 2 hours on Days 0 and 1. The thiotepa was calculated to the nearest milligram.

The peripheral blood hematopoietic cells were to be thawed and re-infused at least 48 hours after the last dose of thiotepa, and filgastrim was to be given daily at a dose of 5 mcg/kg SQ commencing 24 hours after the infusion of the cells, until the ANC was greater than 2,000/ μ L following recovery from the neutrophil nadir.

Dose assignments for the thiotepa were assigned within three days of commencing Consolidation. Consolidation consisted of three cycles at 21-day intervals. Patients began the first cycle of Consolidation when the ANC exceeded 750/ μ L and platelet count exceeded 75,000/ μ L. Subsequent cycles were scheduled to start at least 21 days following Day 0 of the previous cycle and only if the ANC exceeded 750/ μ L and platelet count exceeded 30,000/ μ L for three days without transfusion support. Chemotherapy was delayed until these criteria had been met. The definition of hematopoietic recovery following the third and final Consolidation cycle was an ANC exceeding 500/ μ L, WBC exceeding 1,000/ μ L, and a platelet count exceeding 20,000/ μ L for three days without transfusion; and hemoglobin > 8 g/dL without need for a transfusion.

Carboplatin dose modifications for subsequent courses of Consolidation were modified in the face of specific toxicities. If the GFR or CrCl (performed as a 12-hour study in a hydrated, catheterized patient) was greater than 100 mL/min/1.73m², full dose carboplatin was to be given. If the GFR or CrCl was between 50 and 100 mL/min/1.73m², the dose of carboplatin was to be adjusted based on a modified Calvert formula, to achieve an area under the concentration versus time curve (AUC) of 7/day of treatment or the dosage as calculated

per kilogram, whichever was determined to be lower. If the GFR or CrCl was below 50 mL/min/1.73m², the carboplatin was omitted for that cycle. If hematologic criteria for beginning the next cycle of Consolidation had not been met by day 28, the subsequent carboplatin dose was decreased by 30%. If hearing loss was equal to or greater than 20 decibels at 500 to 4,000 Hz in either ear, the audiogram was to be sent to the Study Chair or Vice-Chair and a decision about dose reduction was to be determined. There were to be no modifications of carboplatin doses for hearing loss above 4,000 Hz.

The peripheral blood hematopoietic cells were to be thawed and re-infused at least 48 hours after the last dose of thiotepa, and G-CSF was to be given daily at a dose of 5 mcg/kg SQ commencing 24 hours after the infusion of the cells, until the ANC was greater than 2,000/uL following recovery from the neutrophil nadir.

The definition of hematopoietic recovery following the third and final Consolidation cycle was an ANC exceeding 500/ μ L WBC exceeding 1,000/ μ L, and a platelet count exceeding 20,000/ μ L for three days without transfusion; and hemoglobin > 8g/dL without need for a transfusion.

This treatment regimen is shown below (Figure 2b):

One primary goal of the study was to determine the maximum tolerated dose (MTD) of thiotepa, so that if dose-limiting pulmonary, hepatic or neurologic toxicities did occur, the Study Chair was to be notified and a determination was to be made if the conditions for MTD had been met. If oropharyngeal mucositis requiring intubation occurred, the subsequent thiotepa dose was to be decreased by 30%.

Biostatistical Considerations: Primary End-Points for Monitoring of Toxicity

An inter-patient dose escalation of thiotepa was performed in the following manner. The dose level was assigned within three working days prior to beginning Consolidation. Once assigned, an individual patient would receive the same dose of thiotepa for each Consolidation cycle unless a decrease in dose was required because of toxicity. Toxicity experienced during all three Consolidation cycles was used to determine the tolerability of a dose level. The events or toxicities occurring after the beginning of Consolidation were defined as dose-limiting toxicities (DLT) associated with thiotepa administration. The escalation algorithm was designed to select the highest thiotepa dose level with high probability that this dose was truly associated with less than 10% levels of thiotepa-related DLT. If the highest thiotepa dose level had a DLT rate exceeding 10%, the algorithm would most likely select a thiotepa dose level with DLT rate between 10% and 20%. The first cohort of patients was started at dose level 1, which allowed for an additional cohort to enter the trial at a thiotepa dose 20% less than the first dose level (referred to as dose level 0), thus allowing the study to accrue patients to answer the study questions if the MTD was over-estimated and during the time period when the toxicities were being evaluated.

The occurrence of toxic death any time during therapy was monitored continuously. An overall toxic death rate of >10% was considered unacceptable. A Bayesian monitoring rule with prior density *Beta* 1,3 on the probability *p* of toxic death was used as a trigger for

careful assessment of toxic death events. This prior density was chosen to reflect the reasonable belief that the toxic death rate would be less than 50%. The prior has median 0.20 and mean 0.25 with approximately 90% of support less than $p=0.55$. A posterior probability $P(p > .10/\text{data}) > 1-n/4N$ would satisfy the monitoring criterion, where n is the interim sample size and $N=32$, the projected minimum sample size. This represents 95% certainty that the toxic death rate exceeds 10% when $n=6$, 75% certainty when $n=32$ and 59% certainty when $N=56$, given the data and the assumed prior density. From a frequentist viewpoint, this criterion will be satisfied 8% of the time when $p=0.05$, and 90% of the time when $p=0.20$, assuming the minimum sample size of $N=32$. The criterion would be satisfied 13% of the time when $p=.05$ and 99% of the time when $p=.20$ assuming the maximum sample size of $N=56$. Operationally, the monitoring criterion would be satisfied if 2 toxic deaths occur in the first 6 patients, 3 in the first 17, or 4 in the first 31 or 5 in the first 46 patients. Early monitoring points would reflect mostly patients who had completed Induction. Later times would reflect also the experience with Consolidation. If the monitoring criteria were satisfied, the detailed analysis would comprise at minimum: a clinical review of the cause and timing of toxic deaths, and a statistical analysis of the toxic deaths and their relationship to either Induction phase alone or to the Consolidation phase.

In addition to the thiotepa dose-limiting toxicities, the following grade IV toxicities were also monitored; ototoxicity, electrolyte wasting and hemorrhagic cystitis. The occurrence of any of these toxicities as well as the DLTs listed in Table 5 was evaluated after the 20th patient. Bayesian monitoring rule with prior density *Beta* 1,3 on the probability p of DLT was used as a trigger for a detailed analysis of the toxicity profile of the treatment regimens. This prior density is identical to that described above, and was chosen to reflect the reasonable belief that the rate of DLT would be less than 50%. Evidence that the overall rate of DLT would exceed 20%, as reflected by a posterior probability $P(p > .20/\text{data})$ greater than 0.95, would satisfy the monitoring criterion. Operationally, the occurrence of more than eight of 20 DLTs would satisfy the monitoring criterion.

These primary endpoints for the analysis of toxicity focused on estimating the overall rates of these toxicities for Induction and for each cycle of Consolidation. Estimates were obtained using life-table methods with an event defined as the first occurrence of toxicity. Patients with progression or recurrence of disease were censored in these analyses. The precision of these estimates can be approximated as an analysis of binomial proportions. If greater than 80% of patients would survive disease-free through the end of therapy, a minimum of 16 patients would be expected to contribute to the estimation of the percentage of patients who experienced toxicity at the selected thiotepa dose. This would provide standard errors of $\pm 5.3\%$ overall and $\pm 7.5\%$ based on an underlying rate of dose limiting toxicity of 10%.

The endpoints for treatment efficacy were (1) event-free survival (EFS), defined as the first occurrence of death by any cause, progression or recurrence of disease, or occurrence of a second malignant neoplasm, measured from the time of study entry, and (2) complete response (CR), defined as the complete disappearance of radiographic and CSF cytological evidence of disease at the completion of protocol therapy (i.e. following recovery from Consolidation). The precision of the estimate of the CR rate and 1-year EFS were

approximated based on simple estimates of a binomial proportion. With a minimum of 20 patients and an underlying CR rate or 1-year EFS of 75%, the standard error of the estimate would be $\pm 9.6\%$.

Results

Study Patients

Between May 1998 and April 2004, 94 children between 6 and 36 months of age at diagnosis were enrolled onto the CCG-99703 study. Two patients were subsequently determined to be ineligible; central review pathology for one revealed a low-grade astrocytoma and the enrollment of the other occurred during a period of administrative study closure. The remaining 92 children were treated according to the protocol. Acquisition of data was continued until December 2010.

Demographic and disease characteristics of the 92 eligible patients are summarized in Table 1. The histologic grouping in Table 1 was based on the central review of pathology, when available. Central review was performed on 70 of the 92 eligible patients; nine cases had no slides submitted, five submitted were not reviewed, and the status of eight is unknown. One patient with DIPG did not undergo biopsy as per study. Among the 70 cases with central review, 10 ‘discordances’ reflected a difference in nomenclature that existed at the time: for nine cases with institutional diagnosis of (posterior fossa) PNET the review diagnosis was medulloblastoma, and in one case a third ventricular tumor was institutionally called a medulloblastoma and centrally reviewed as a PNET. Of the remaining 60 cases with centrally-reviewed pathology, discordance was determined in 17 (28.1%), and is shown in Table 2.

Table 3 shows the relationship between the major histologic groups and M-stage. Table 4 shows the relationship between the histologic groups and the extent of surgical resection/residual tumor; no residual tumor along with a gross total resection (GTR) was obtained in 47 of 92 patients (51%). Ependymoma and desmoplastic medulloblastoma patients had the highest proportion of M0 stage (90% and 93% respectively) and ependymoma patients had the highest proportion with no residual tumor following initial surgery (81%).

Induction Chemotherapy

Induction chemotherapy was initiated on all 92 eligible patients. Following surgery for diagnosis and maximal tumor resection (except a single case of DIPG), Induction chemotherapy was started within six weeks in all but one patient, whom, as per study, was re-staged and found to have no residual or recurrent tumor and thus eligible to proceed.

In general, Induction chemotherapy was well tolerated, with major toxicities confined to hematopoietic suppression and related infection. Of the 92 patients that started the Induction phase, 88 began the third cycle, so that 269 of 276 planned cycles of chemotherapy were administered. Eighty-seven patients were hospitalized for toxicity during the Induction portion of the study, and five patients were reported as having no hospitalization days. There was missing information regarding hospitalizations during Induction therapy on six patients.

The median duration of hospitalization for toxicity was 7, 4 and 4.5 days for cycles 1, 2 and 3 respectively.

Table 5 summarizes the cumulative percentage of patients with major grade 3 or 4 toxicities during the Induction and Consolidation phases. Both the incidence and severity of all toxicities were within the expected range for patients treated with this intensity of chemotherapy.

Of 41 patients who were determined by their institution to have measurable residual disease following surgery, 40 completed three cycles of Induction; eight of the 40 (20%) were reported by the institutional radiologists to achieve complete radiographic responses after the Induction phase (four medulloblastoma, three pineoblastoma, one other (choroid plexus carcinoma). Of 35 patients determined by central review to have measurable residual disease following surgery, 10 (29%) demonstrated a complete response.

Adequate peripheral hematopoietic cell collections were achieved on all but two patients, and these two patients did not proceed to Consolidation therapy. The radiographic response to Induction therapy is shown in Table 6a.

Second-Look Surgery

For patients with residual tumor following Induction, there was an option for another surgery before the Consolidation phase for the purpose of reducing the bulk of tumor. Nine patients underwent surgery during this window; six of the nine were alive at last contact. One patient died during surgery of uncontrollable bleeding, despite having a normal platelet count, and two patients subsequently developed progressive tumor following Consolidation.

Consolidation Therapy

Of 92 eligible patients, 11 did not proceed to Consolidation therapy and were not assigned a thiotepe dose, four due to tumor progression, two due to death, three due to parental refusal and two due to failure to achieve adequate peripheral hematopoietic cells from leukapheresis. The two early deaths included one patient who died of disease soon after enrollment without receiving any chemotherapy, and the patient noted above who died of uncontrollable hemorrhage during second-look surgery between Induction and Consolidation. The assigned thiotepe dose and distribution of patients, as well as details of the dose-limiting toxicities during Consolidation, are shown in Table 7. Eighty-one patients received the first cycle of Consolidation (CC1), 78 received the second cycle (CC2) and 72 received the third cycle (CC3). Thus, 231 of 243 planned cycles of Consolidation were administered.

A review of the toxicity at dose level 5 indicated that three of 18 patients experienced a DLT, which indicated that the MTD of thiotepe should be dose level 4 (10 mg/kg/day). There were only three patients with grade 4 ototoxicity and seven patients with grade 3 ototoxicity during Consolidation, although 27 patients had hearing loss >20 dB at 500–4000 Hz in at least one ear during at least one cycle of Consolidation. One patient on dose level 4 experienced grade 4 serum BUN and grade 3 serum creatinine elevations during Consolidation; he subsequently died of multi-organ system failure secondary to septicemia.

Two patients completed all three Consolidation cycles, but failed to do so within the 100 day Study requirement, thus representing DLTs. In both cases, delays in recovering from Cycle #1 (at dose level #3) were responsible; one associated with Gram-negative septicemia and prolonged neutropenia, the second due to erroneous omission of Neupogen administration.

Of 81 patients commencing Consolidation marrow-ablative chemotherapy, 35 had measurable residual tumor per institutional data at baseline, of whom 31 completed three cycles. Of these 31 patients, four achieved a CR and 6 sustained a CCR by the end of Consolidation. Based on the central review data, 32 of the 81 patients who began Consolidation had measurable residual tumor; 27 completed three cycles, nine of whom achieved CR at the end of Consolidation. The radiographic response to Induction therapy is shown in Table 6b.

Deaths Possibly Associated with Treatment

There were five deaths that occurred in which a contributory role for study chemotherapy merited consideration. Two patients experienced toxic deaths during study therapy (Table 7). One additional patient developed a cardiac arrest while receiving reinfusion of autologous peripheral hematopoietic cells during Consolidation, and rapidly expired; this was initially considered to be a toxic death, but upon autopsy, extensive brainstem involvement with tumor was considered the cause of the cardiac arrest, and death thereby was attributed to tumor progression. There were two additional deaths that arose among study patients, remotely related to study therapy. One patient died of an intracranial hemorrhage as a complication of “second-look” surgery following recovery from Induction chemotherapy without evidence of thrombocytopenia or a coagulation defect (as previously described). One patient had been removed from the protocol for failure to obtain adequate peripheral hematopoietic cells at leukapheresis, and later died from complications of treatment-induced renal toxicity and hemorrhage in the face of progressive tumor.

Event-Free And Overall Survival: All Patients

Median and mean follow-up time among patients without treatment failure is 9.0 and 8.7 years, respectively. Overall survival (OS) and event-free survival (EFS) are shown in Table 8 for the 92 eligible patients. At 5 years from study entry, the OS rate was $63.6 \pm 5\%$ and the EFS rate was $43.9 \pm 5.2\%$.

Multivariate Cox regression analyses were performed to assess the relative independent significance of the variables in Table 8 as predictors of EFS and OS. Gross total resection (GTR) with no residual tumor was the strongest significant predictor of EFS; the relative risk (RR) of an event was 2.7 higher for those with GTR/no residual tumor than for those without GTR/residual tumor (95% C.I.: 1.43 to 5.07, $p = .002$). Male patients were at 2.1 times increased risk (95% C.I.: 1.12–3.86, $p = .02$) of an event compared to female patients. Other factors were not statistically significant. For OS, the presence of residual tumor was the only predictor that was statistically significant.

Figures 3a and 3b provide EFS and OS data for the major histologic groups. OS (log rank $p = .034$), but not EFS, differed significantly by histologic group, with ependymomas having the highest 5-year OS rates ($81.0 \pm 8.6\%$). However, patients with ependymoma had the

highest percent of M0 patients, as shown in Table 3 and the highest percent of patients with gross total resection with no residual tumor, as shown in Table 4.

Event-Free And Overall Survival: Medulloblastoma

Among the 36 patients with medulloblastoma, the 1-, 2-, and 5-year EFS rates were 71% $\pm$ 8%, 60% $\pm$ 8%, and 60% $\pm$ 8%, respectively. Medulloblastoma patients underwent central pathology review specifically to determine the presence or absence of the desmoplastic variant. Of 36 medulloblastoma patients, 32 were reviewed, of whom 14 were desmoplastic and 18 were non-desmoplastic. The EFS and OS are presented in Table 9; the 5-year EFS and OS for those with desmoplastic medulloblastoma are 78.6 $\pm$ 11% and 85.7 $\pm$ 9.4%, *versus* 50.5 $\pm$ 11.8% and 60.6 $\pm$ 11.6% for non-desmoplastic MB ($p = .038$ and $.046$, respectively). Only one of 14 desmoplastic medulloblastoma patients was M1+, while eight of 18 non-desmoplastic medulloblastomas were M1+. The single metastatic desmoplastic medulloblastoma patient developed recurrent disease, while 37.5 $\pm$ 17.1% of M1+ non-desmoplastic medulloblastomas were event-free survivors at five years.

Multivariate analysis show that gender, presence of metastatic disease and residual tumor were significant prognostic factors in predicting EFS. The RR for an event was 7.38 times (95% C.I.: 1.18 – 46.36, $p = .03$) higher for the patients with metastatic disease than for those without metastatic disease. The RR of an event was 4.88 higher for those with no GTR/residual tumor than for those with GTR/no residual tumor (95% C.I.: 1.26 to 18.9, $p = .002$). The RR for an event was 9.47 times (95% C.I.: 1.72–52.24, $p = .01$) higher for the male patients than for female patients. The multivariate analysis of OS showed that gender and presence of metastatic disease were significant prognostic factors in predicting OS.

Of the 23 medulloblastoma patients known to be living at most recent follow-up (median and mean of 9.0 and 8.7 years, range 3.7 to 11.6 years from study enrollment) 11 never received irradiation, five received irradiation without prior tumor recurrence, two received irradiation following development of tumor recurrence at 6 weeks and 18 months from diagnosis (alive 10.8 and 8.4 years post-recurrence, respectively) and for six no information is available as to irradiation status. Twenty of the 23 surviving medulloblastoma patients underwent central pathology review; ten had desmoplastic histology; none of the desmoplastic survivors relapsed; only one surviving desmoplastic medulloblastoma was known to have received irradiation.

Event-Free And Overall Survival: Ependymoma

The 1- and 5-year EFS rates for ependymoma were 86% $\pm$ 8% and 38% $\pm$ 11%, respectively. Of the 15 ependymoma patients known to be living at most recent follow-up, three never received irradiation, six received irradiation without prior recurrence and six received irradiation following development of tumor recurrence. Central pathology review was accomplished on 12 of 15 surviving patients; eight were reviewed as cellular ependymomas (seven known to have received irradiation) and four as anaplastic ependymomas (two known to have received irradiation and two known not to have received irradiation). Two of seven surviving children with supratentorial ependymoma and one of 10 surviving children with posterior fossa ependymoma continue relapse-free without irradiation. Median and mean

duration of follow-up for surviving patients was 9.9 and 9.3 years respectively, ranging from 4.3 to 11.9 years. Median and mean duration of follow-up from relapse in the six surviving patients is 5.9 and 6.1 years, ranging from 3.0 to 10.1 years .

Event-Free And Overall Survival: Pineal And Non-Pineal PNET

The supratentorial PNET patients (eight pineal and nine non-pineal) were analyzed separately. The 1- and 5-year EFS rates for supratentorial PNET were $35\% \pm 12\%$ and $29\% \pm 11\%$, respectively. Of the seven PNET patients known to be living at most recent follow-up (median and mean follow-up of 8.7 years, ranging from 5.9 to 11.2 years), three were not known to have received irradiation, two received irradiation following tumor recurrence, and one received irradiation without prior tumor recurrence for residual tumor.

Event-Free And Overall Survival: AT/RT

The 1- and 5- year EFS rates for AT/RT were $37.5\% \pm 17\%$ and $37.5\% \pm 17\%$, respectively. Of the eight AT/RT patients (five infratentorial and three supratentorial), all of whom had non-metastatic disease (M0) at diagnosis, four patients survive. Three of the survivors initially underwent less than gross total resections. Primary tumor locations of the surviving patients were infratentorial in two and supratentorial in two. Ages at diagnosis of surviving patients were between 20 and 32 months. One survivor never received irradiation (posterior fossa in primary location), one received whole posterior fossa irradiation without prior tumor recurrence and two received focal irradiation following development of tumor recurrence (at 11 and 12 months from study enrollment). All surviving patients have most recent follow-ups between 8.1 and 11.9 years (mean 9.6 years) from study enrollment and/or subsequent recurrence.

Event-Free And Overall Survival: Other Eligible

The 1- and 5- year EFS rates for “other eligible” were $60\% \pm 15\%$ and $30\% \pm 15\%$, respectively. Of the 10 patients with centrally confirmed “other eligible” diagnosis, only three survive. Two (of the four enrolled) children with choroid plexus carcinoma survive without disease at 7.9 and 4.9 years, one following irradiation at tumor recurrence (now 6.7 years from recurrence) and the other without receiving irradiation. A third patient with a centrally reviewed diagnosis of anaplastic astrocytoma (located in the cerebellar hemisphere, and having undergone a gross total resection without residual tumor), survives 5.5 years from diagnosis at most recent follow-up without receiving irradiation.

Discussion

Some 30 different malignant histologic types of CNS tumors (as classified by the WHO) are found in young children, and a variable response can be expected with any one specific treatment regimen.¹⁴ Apart from medulloblastoma, the most common malignant CNS tumor in young children, the incidence of any other histologic tumor type is sufficiently rare to preclude conduct of controlled randomized clinical trials restricted to a particular histopathological diagnosis. The justification for conducting this trial to include all malignant histologies was that survival for all these tumor types had been poor, and

radiotherapy, previously a component of standard treatment, was recognized to produce unacceptable side-effects in survivors.

Outcomes of prior brain tumor trials in young children had suggested that chemotherapy-based strategies were reasonable approaches to treatment, as they had demonstrated some modest success in avoiding or at least delaying the use of radiotherapy.^{3, 10, 11, 12, 13, 15, 16, 17} In addition, when initial surgical attempts at tumor resection were not possible or gave less than gross total resections, chemotherapy was able to reduce the tumor bulk in some patients so that a second surgical procedure could be attempted, potentially allowing for greater effectiveness of additional treatment.¹⁸ The use of high-dose, marrow-ablative chemotherapy with autologous bone marrow or hematopoietic cell rescue had also shown some efficacy at treating children with recurrent malignant brain tumors and young children with newly-diagnosed malignant brain tumors.^{19, 20, 21, 22, 23} The limitations of using autologous marrow support in young children included the technical aspects of harvesting autologous hematopoietic cells and the lack of experience in using marrow-ablative chemotherapy in these younger children. The technological advances in the immediate years preceding this study allowed for the trial design, yet safety data of this therapy in the cooperative group setting were still unavailable.

Four previously published cooperative group North American trials had attempted to either delay irradiation (Baby POG-1³) or avoid irradiation (CCG-921¹⁰ for CNS embryonal tumors, CCG-945¹⁵ for malignant glial tumors and CCG-9921¹³ for all CNS malignancies) by using standard-dose chemotherapy regimens from 12 to 36 months' duration. In the POG study, 1- and 2-year progression-free survivals (PFS) were 42% and 34% for those with medulloblastoma, and 45% (1-year) and 37% (2-year) for the entire cohort.³ In those studies attempting to avoid irradiation with standard-dose chemotherapy alone, high failure rates were observed particularly in those children with residual post-operative tumor, as well as in children with leptomeningeal dissemination to the brain and/or spinal cord (M1+ disease).^{3, 10, 13, 15}

In the CCG-921 study, young children treated only with the "8-drugs-in-1-day" chemotherapy regimen experienced a 3-year PFS of 29% for those without metastases and only 11% for those with metastases. The 3-year PFS for all medulloblastoma patients on CCG-921 was 22%.¹⁰

The CCG-9921 study, conducted between 1993 and 1997, was the immediate forerunner of the current CCG-99703 study. This study compared two regimens, both including five cycles of standard intensive Induction chemotherapy, to compare response and tolerance of the Induction regimens; both Induction regimens were followed by a common 'maintenance' regimen of chemotherapy of just over 12 months' duration. There were no significant differences in response rates or EFS between the two Induction regimens; however, Regimen A was considered less toxic, and thus served as the basis for the CCG-99703 Induction regimen.¹³

The Head Start I study, conducted between 1991 and 1997 at a limited set of institutions, employed five cycles of intensive but standard-dose Induction chemotherapy, based upon

and virtually identical with Regimen A of the CCG-9921 study, followed by a single cycle of marrow-ablative chemotherapy (thiotepa, etoposide and carboplatin) with autologous hematopoietic cell rescue (derived from either bone marrow or peripheral blood). This study, the outcomes for which were published in 1998, provided the basis for the use of autologous hematopoietic cell rescue in the CCG-99703 study.¹¹

After a maximal surgical resection and staging, patients were treated with the same Induction chemotherapy Regimen A as CCG-9921¹³ and the virtually identical Head Start I Regimen A¹¹; this served both a therapeutic goal of tumor cytoreduction, as well as a method by which to harvest adequate peripheral hematopoietic cells over the course of three cycles. The Induction treatment chosen was considered a standard therapy, with a known response rate.¹³ For patients with residual bulk tumor, the option of a second surgical resection was permitted, as extent of surgical resection had previously been shown to be a positive predictive measure of outcome.^{24, 25} At the time of initial development of this study, there were few pediatric centers with the technology and experience to perform peripheral blood leukapheresis in young children; therefore, the trial was initially planned to be limited to only CCG Phase I institutions. However, by study opening, many institutions had become adept in peripheral blood leukapheresis in young children, and the study was amended to permit any CCG institution with the technology and experience to enroll patients. A total of 36 institutions opened the CCG-99703 trial open and thus were prepared to enroll patients. Twenty-five institutions enrolled patients on this study, with up to six patients per institution.

A feature of the trial design, necessary to ensure absence of excessive toxicity with each thiotepa dose escalation, required study closure to new patient accrual during each cohort analysis. To hasten enrollment, the second cohort of patients were treated with a smaller dose of thiotepa than the first cohort, and when the first cohort cleared toxicity analysis, the third cohort was enrolled at the next higher dose level. Each cohort consisted of six patients, with each cohort of patients accruing quickly. The toxicity analyses could not occur until the end of Consolidation, which was a minimum of 15 weeks' (105 days) duration from its onset; because of study permissible delays, such as second-look surgery, duration actually extended to as long as 252 days (a mean 153 days). Therefore the time between the last patient registering on study within one cohort and the time until the next cohort could enroll patients took about six months, sometimes longer. Patient accrual during the times the study was open was brisk; this resulted in a bias to larger institutions (or those caring for more brain tumors) to have patients during the time the study was actually open for patient enrollment to occur. We have no estimate how many children were treated using this treatment outside of study enrollment. Had the trial design allowed for continuous enrollment, we would have expected to enroll more patients from additional institutions. Regardless, the number of institutions participating in this trial underscores one element of its success.

Another measure supporting the success of the first study goal is that the treatment was tolerated by patients within acceptable limits, there were no adverse events that could be considered unexpected, and there were no systematic errors or problems with the trial design. There were 92 patients that enrolled on this trial, 81 that started Consolidation and 71 that completed all three cycles of Consolidation. There were five deaths that occurred

while children were on the study, but only two of these deaths could be viewed as a result of the Consolidation portion of the study (one at dose level 1, one at dose level 4) due to fungal infections, one associated with ARDS. Only one child was removed from the study because of inadequate peripheral hematopoietic cell harvest, and died of progressive disease, but with what was likely Induction-therapy induced renal toxicity and bleeding. One child died of uncontrolled hemorrhage during the second-look surgery and another of progressive brainstem tumor during the Consolidation phase. Fatal treatment-related toxicity is an unfortunate but expected consequence of marrow-ablative chemotherapy; however, the CCG-99703 toxic mortality rate of 2/81 patients (2.5%) and 2/230 marrow-ablative cycles (0.87%) represent lower mortality rates than were reported for the marrow-ablative single-cycle regimens on the Head Start I trial.¹¹ Of note, however, two of 81 patients (2.5%) on CCG-99703 were unable to complete all three marrow-ablative cycles due to incomplete hematopoietic recovery following Consolidation cycles.

The study was opened to all malignant histologic types of brain tumor and not designed to provide survival data for any particular tumor type. The nature of the entry criteria could have selected against the infants that had major neurological or surgical complications, one form of investigator bias. Therefore the survival data needs to be viewed in the context of how patients may have been accrued for the study. This trial was also not primarily designed to investigate the role of radiotherapy, and irradiation in those patients following completion of the study and prior to relapse likely altered the EFS and OS. There was no intent of the trial design to encourage or discourage the use of radiotherapy as a Consolidation therapy, although investigators were required to report any post-study event such as relapse, death or the use of radiotherapy.

Comparison of CCG-99703 with CCG-9921

CCG-99703 was compared to a similar cohort of 256 patients from CCG-9921, which was open to accrual between 1993 and 1997; standard dose chemotherapy (without marrow-ablative Consolidation chemotherapy) and deferred radiotherapy were given to infants younger than 36 months with malignant brain tumors. CCG-9921 infants under 6 months of age were excluded from this comparison since that age group was not included in CCG-99703. The demographics of the two studies were comparable after the age exclusion. No significant differences in frequency distribution were found based on age, sex, M-stage, histologic diagnosis, or tumor site. However, there was a significant difference based on extent of resection/amount of residual tumor; a greater percent of patients on CCG-99703 had gross total resection with no residual tumor compared to CCG-9921 (Fisher exact $p = .002$).¹³ (This may be because the results of 9921 and other similar studies pushed investigators to attempt more GTRs in the CCG-99703 study patients.) Based on patients with gross total resection, differences in overall survival and event-free survival were found between CCG-99703 and CCG-9921 ($p = .03$ for OS and $p = .002$ for EFS); however, no differences between the studies were found based on patients with residual tumor.¹³

Figures 4a and 4b show EFS and OS curves for the 92 eligible CCG-99703 patients and the 256 patients on CCG-9921 older than 6 months. EFS and OS for CCG-99703 patients are significantly higher than for CCG-9921 patients. The 5-year EFS for CCG-99703 are 44

$\pm 5\%$ *versus* $26 \pm 3\%$ for CCG-9921 (log rank $p = .002$). The 5-year OS for CCG-99703 are $63 \pm 5\%$ *versus* $43 \pm 3\%$ for CCG-9921 (log rank $p = .011$).

In the CCG-9921 study¹³, the overall response rate to Induction chemotherapy was 42% (compared with 64% in the current CCG-99703 study). The 5-year EFS of CCG-9921 for individual histologic tumor types can be only loosely compared with that of the CCG-99703 study. Nevertheless, 5-year EFS in CCG-9921 *versus* CCG-99703 appears improved in CCG-99703 for children with medulloblastoma ($32 \pm 5\%$ *versus* $60 \pm 8\%$), although this difference is not observed for the subset of patients with desmoplastic medulloblastoma ($77 \pm 9\%$ *versus* $79 \pm 11\%$). No differences in 5-year EFS were observed for other PNET ($17 \pm 6\%$ *versus* $29 \pm 11\%$), for ependymoma ($32 \pm 6\%$ *versus* $38 \pm 11\%$) and for AT/RT ($14 \pm 7\%$ *versus* $38 \pm 17\%$). Of patients surviving beyond 5 years from diagnosis, 58% on CCG-9921 and 56% on CCG-99703 had never received irradiation by the time of most recent report.

Comparison of CCG-99703 with Head Start I Study

The Head Start I trial was conducted between 1991 and 1995, with preliminary data available at the time of CCG-99703 study development. It was already clear that the Head Start I Induction and Consolidation regimens were both more toxic than previous chemotherapy regimens for childhood brain tumors, with reported a toxic mortality rate during five cycles of Induction of 6% and during the single marrow-ablative Consolidation cycle of 8%.¹¹ A major hypothesis of the CCG-99703 study would be that a shorter number of Induction cycles (three *versus* five) followed by three “mini” tandem Consolidation cycles rather than a single heavier dose marrow-ablative Consolidation cycle, would prove at least as effective and have less toxic mortality. This hypothesis is suggested in the current report, with no toxic deaths in Induction and a 2.6% toxic mortality rate in Consolidation.

A comparison of impact of CCG-99703 *versus* Head Start I upon on EFS and OS, can only be very loosely made. However, there are no apparent significant outcome differences in major disease groups between Head Start I¹¹ and CCG-99703.

Outcome for Patients with Desmoplastic versus Non-Desmoplastic Medulloblastoma

It has become increasingly recognized over the last decade that the desmoplastic/nodular variants of medulloblastoma are more common than had been previously appreciated in young children with medulloblastoma, and that this pathologic subtype is predictive of a superior survival rate.^{26, 27, 28, 29} The 5-year EFS and OS for desmoplastic medulloblastoma on CCG-99703 were $78.6 \pm 11\%$ and $85.7 \pm 9.4\%$, compared with $50.5 \pm 11.8\%$ and $60.6 \pm 11.6\%$ for non-desmoplastic medulloblastoma ($p = .038$ and $.046$, respectively). This encouraging outcome for desmoplastic medulloblastoma on CCG-99703 may be loosely compared with those reported from CCG-9921^{13, 29}, Head Start I¹¹, as well as more recent trials (HIT SKK 92, Head Start III) with 5-year EFS ranging from 67% to 89%.^{28, 29}

Comparison With More Recently Completed Prospective Trials For Young Children With Malignant Brain Tumors And Development Of Current COG Trials

In the years since CCG-99703 was initiated, a limited number of prospective multi-center therapeutic studies in young children with malignant brain tumors have been conducted and reported. The Head Start II and III studies built upon the initial Head Start I study through the addition of high-dose systemic methotrexate to the Induction chemotherapy regimen^{29, 30, 31, 32, 33} The German-speaking countries' HIT SKK trial added both systemic and intraventricular methotrexate, but without use of marrow-ablative chemotherapy.²⁶ The French (BB-SFOP) study used initial standard-dose Induction chemotherapy, and relied upon marrow-ablative chemotherapy to successfully rescue a substantial proportion of patients at recurrence^{34,35}. These studies have repeatedly reaffirmed the prognostic advantage of radical resection of the primary tumor and absence of metastatic disease at diagnosis, as well as the highly favorable prognostic significance of the desmoplastic/nodular variant of medulloblastoma. One recently published North American study (POG-9934) utilized four months of conventional chemotherapy for children less than 3 years old with localized MB followed by posterior fossa irradiation (18Gy-23.4Gy) with tumor bed boost and subsequent maintenance chemotherapy. The 4-year EFS and OS were only $50 \pm 6\%$ and $69 \pm 5.5\%$ respectively, and even for desmoplastic/EN histology, EFS was only 58.8%. Furthermore, 15 of 19 patients relapsing post-irradiation did so *outside* the primary site of irradiation.³⁶ This study reinforces concerns of using just focal irradiation in conjunction with non-marrow-ablative chemotherapy in young children with even localized medulloblastoma.

Building upon the preliminary results of the CCG-99703 study, the use of high-dose systemic methotrexate in the German and Head Start II trials has been incorporated into the current COG trial for young children with high-risk (i.e. metastatic and/or local residual) medulloblastoma, comparing the CCG-99703 Induction with or without the addition of high-dose systemic methotrexate. In addition, the use of high-dose methotrexate in the Head Start II trial for AT/RT³⁷ have led to the development of a COG trial for AT/RT including high-dose methotrexate in Induction followed by CCG-99703 Consolidation marrow-ablative chemotherapy. On the other hand, the favorable outcome for young patients with desmoplastic/nodular medulloblastoma is generating reduced therapy options in new clinical trials under development internationally.

Since the completion and closure of this trial, molecular profiling has led to the recognition of 4 distinct sub-types of medulloblastoma; the *Sonic Hedgehog (Shh)* pathway sub-group is particularly prevalent in young children, and is largely but not exclusively found in patients with desmoplastic/nodular histology and is associated with a favorable outcome³⁸. However, a formal prospective evaluation of the prognostic significance of the molecular sub-classifications in young children with medulloblastoma has yet to be reported.

Conclusions

The goals of this prospective multi-center study for young children (less than 36 months of age) with newly diagnosed malignant brain tumors have been accomplished. The brief Induction regimen followed by the innovative sequential tandem marrow-ablative

chemotherapy cycles, each with autologous hematopoietic cell rescue, resulted in acceptable morbidity and mortality and is feasible for the majority of patients in the cooperative group setting. A maximally tolerated dose for thiotepa of 10mg/kg/day x 2 days in conjunction with a fixed dose of carboplatin was carefully defined in a fixed phase I design. This study, based upon the findings reported, now serves as the basis for current ongoing COG studies for young children newly-diagnosed with medulloblastoma, other PNET and ATRT.

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Figure 1.
Treatment Schema

Figure 2.
 Figure 2a: Induction Chemotherapy Schema
 Figure 2b: Consolidation Chemotherapy Schema

Figure 3.

Figure 3a: K-M Plot EFS major histologic groups

Figure 3b: K-M Plots OS major histologic groups

Figure 4.

Figure 4a: K-M EFS 99703 *versus* 9921 age > 6 months

Figure 4b: K-M OS 99703 *versus* 9921 age > 6 months

Patient Characteristics

Table 1

	Characteristic	Number	%	Characteristic	Number	%
Gender	Male	46	50	Residual Tumor	47	51.0
	Female	46	50	None/Not Visible	10	10.9
Age	6–11 mo	13	14.1	1.5 cm ²	21	22.8
	12–17 mo	22	23.9	> 1.5cm ²	11	12.0
	18–23 mo	23	25.0	Tumor not Measurable	3	3.3
	24–29 mo	15	16.3	Equivocal/Unknown		
	30–35 mo	19	20.7			
Race				Extent of Resection	1	1.1
	White	61	66.3	No biopsy	4	4.3
	Hispanic	16	17.4	Biopsy (<10%)	6	6.5
	Black	9	9.8	Partial (10–49%)	19	20.7
	Other/Unknown	6	6.5	Subtotal (50–95%)	10	10.9
				Near total (>95–<100%)	52	56.5
M-Stage				Gross total (100%)		
	M0	67	72.8			
	M1+	22	23.9	Histologic Group		
	Unknown	3	3.3	Medulloblastoma (non-desmoplastic)	22	23.9
				Medulloblastoma (Desmoplastic)	14	15.2
				Ependymoma	12	13.0
				Ependymoma, Anaplastic	9	9.8
				SPNET, Non-pineal	9	9.8
				SPNET, Pineal (pineoblastoma)	8	8.7
				AT/RT	8	8.7
				Other Eligible*	10	10.9

* Other Eligible diagnoses included choroid plexus carcinoma (n=4), anaplastic astrocytoma (n=1), glioblastoma (n=1), DIPG (n=1), pineal region medulloblastoma (n=1), ATRT (1 by institutional report) and PNET (1 by institutional report)

Table 2

Discordant Institutional and Central Pathology

Institutional Pathology	Central Review Pathology	Number
Medulloblastoma	Medulloblastoma - desmoplastic	7
AT/RT	Supratentorial PNET	2
Ependymoma	Ependymoma - anaplastic	2
Ependymoma - anaplastic	Ependymoma	2
Medulloblastoma - desmoplastic	Medulloblastoma	1
PNET (Ganglioneuroblastoma)	Other Eligible (Medulloepithelioma)	1
Other Eligible	Ependymoma	1
Supratentorial PNET	Other Eligible Diagnosis	1

Table 3

Major Histologic Groups by M-Stage

	M0	M+	Unknown	Total
Meduloblastoma				
Not Desmoplastic	10 (56%)	8 (44%)	0 (0%)	18 (100%)
Desmoplastic	13 (93%)	1 (7%)	0 (0%)	14 (100%)
Unknown	3 (75%)	1 (25%)	0 (0%)	4 (100%)
Ependymoma				
Not Anaplastic	11 (92%)	1 (8%)	0 (0%)	12 (100%)
Anaplastic	8 (89%)	0 (0%)	1 (11%)	9 (100%)
PNET				
Non-pineal	6 (67%)	3 (33%)	0 (0%)	9 (100%)
Pineal	4 (50%)	4 (50%)	0 (0%)	8 (100%)
AT/RT	7 (88%)	0 (0%)	1 (12%)	8 (100%)
Other	5 (50%)	4 (40%)	1 (10%)	10 (100%)
Total	67	22	3	92

Table 4

Major Histologic Groups by Gross Total Resection (GTR)/Residual Disease

	GTR and NO Residual disease	Less than GTR or Residual Disease	GTR and Residual Disease Unknown	Total
Medulloblastoma				
Not Desmoplastic	9 (50%)	7 (39%)	2 (11%)	18 (100%)
Desmoplastic	9 (64%)	4 (29%)	1 (7%)	14 (100%)
Unknown	2 (50%)	2 (50%)	0 (0%)	4 (100%)
Ependymoma				
Not Anaplastic	8 (67%)	4 * (33%)	0 (0%)	12 (100%)
Anaplastic	9 (100%)	0 (0%)	0 (0%)	9 (100%)
PNET				
Non-pineal	4 (44%)	5 (56%)	0 (0%)	9 (100%)
Pineal	1 (12%)	7 (88%)	0 (0%)	8 (100%)
AT/RT	2 (25%)	5 (63%)	1 (12%)	8 (100%)
Other	3 (30%)	7 ** (70%)	0 (0%)	10 (100%)
Total	47	41	4	92

* All 4 were of infratentorial location.

** Includes the single unbiopsied Diffuse Intrinsic Pontine Glioma.

Table 5

Grades 3 and 4 Toxicities During Therapy

Toxicity	Induction (%)	Consolidation (%)
Hematologic	100	98.8
Infection	55.4	54.4
Gastrointestinal - stomatitis	14.5	25.8
Nervous system	9.9	9.0
Hearing (objective)	6.7	12.7
Pulmonary (clinical)	6.7	9.1
Fever	4.4	3.9
Hyperbilirubinemia	2.3	6.3
Weight Change	2.3	1.2
G-CSF induced discomfort	2.2	0
Renal - azotemia	1.1	1.3

Table 6a

Response After Induction by Central Pathology and Central Radiology Review

Central Pathology	Induction Response (Central Radiology Review)									
	Un known	CR	MR	NE	NE/ND	NE/PI	PD	PR	SD	Total
AT/RT	0	2	0	1	2	0	0	2	1	8
Ependymoma	0	8	1	0	8	0	1	0	3	21
Medulloblastoma	0	16	1	1	8	0	2	5	3	36
Other	1	2	0	0	2	0	1	1	3	10
PNET	0	1	0	1	5	0	1	1	0	9
Pineoblastoma	0	3	0	0	3	1	0	3	0	8
Total	1	30	2	3	28	1	5	12	10	92

Table 6b

Response after Consolidation by Central Pathology and Central Radiology Review

Central Pathology	Central Radiology Review									
	Unknown	CCR	CR	MR	NE	NE/ND	PD	PR	SD	Total
AT/RT	0	1	1	0	1	2	0	0	2	7
Ependymoma	0	2	5	2	1	7	1	1	1	20
Medulloblastoma	0	4	11	0	0	9	2	1	5	32
Other	0	0	2	0	0	0	1	2	1	6
PNET	1	0	1	0	1	2	2	1	0	8
Pineoblastoma	1	0	2	0	0	5	0	0	0	8
Total	2	7	22	2	3	25	6	5	9	81

Table 7

Summary of Evaluability and Types of DLTs During Consolidation

Dose Level	Thiotepa Dose (mg/kg/day)	Eligible Patients	Number Evaluable for DLT	Number Inevaluable for DLT	Reason Inevaluable	Number of DLTs	DLT
-	Not assigned	11	0	11	No Consolidation No dose level**	-	
0	5	11	11	0		0	
1	6	13+	13	0		1	Toxic Death (Candida, ARDS) in CC3
2	7.2	11	10	1	Withdrawn by parent in CC1	1	Neurologic Grade 4 toxicity (CC3)
3	8.4	13+	13	0		3	1 Severe Diarrhea and Vomiting (CC1) 1 Failure to complete 3 cycles; Prolonged pancytopenia (CC1) 1 Failure to complete 3 cycles; prolonged low platelets (CC3)
4	10	14	11	3	1 PD in CC2, 2 withdrawn before CC3	2	1 Hepatic Veno-occlusive Disease (CC3) Toxic Death (fungal sepsis) in CC2
5	12	19	18	1	Died during CC2	3	Pulmonary toxicity Grade 4 (CC2) Pulmonary toxicity Grade 4 (CC2) Veno-occlusive Disease (CC2)
Total		92	76	16		10	

* One patient was inappropriately treated by the institution at this dose level, after thiotepa dose escalation to the next level had been activated.

** There were 11 patients that did not proceed to Consolidation therapy and thus are not eligible for DLT evaluation (see text).

Table 8

Event-Free and Overall Survival Rates Among All Patients.

		5-year EFS				5-year OS			
		# Patients	%	SE	P value*	%	SE	P value*	
All	Eligible	92	43.9	5.2		63.6	5.1		
	< 12 months	13	38.5	13.5		53.9	13.9		
	12–24 months	45	45.3	7.5	.794	63.4	7.3		
Gender	24–36 months	34	44.1	8.5		67.7	8.0	.31	
	Male	46	52.1	7.4		71.6	6.7		
	Female	46	35.6	7.1	.054	55.4	7.4	.052	
M-Stage	M0	67	51.5	6.2		68.2	5.7		
	M1+	22	27.3	9.5	.026	54.6	10.6	.062	
	Missing	3							
Resection	GTR/No Residual	47	54.4	7.3		75.9	6.3		
	<GTR or Residual	41	28.9	7.1	.0065	48.7	7.8	.0034	
	Missing	4							
Site	Supratentorial	32	34.4	8.4		53.1	8.8		
	Infratentorial	60	49.1	6.5	.082	69.1	6.1	.0426	
Histology	Medulloblastoma (all)	36	60.0	8.3		68.3	7.9		
	Ependymoma	21	38.1	10.6		81.0	8.6		
	SPNET/Pineoblastoma	17	29.4	11.1	.163	41.2	11.9	.034	
	AT/RT	8	37.5	17.1		62.5	17.1		
	Other Eligible	10	30.0	14.5		50.0	15.8		

* P values from log-rank test

Table 9

Event-Free and Overall Survival Rates Among Medulloblastoma Patients

		5-year EFS				5-year OS			
		# Patients	%	SE	P value	%	SE	P value	
All		36	60.0	8.3		68.3	7.9		
		26	72.0	9.0		76.0	8.5		
M-Stage	M0	10	30.0	14.5	.007	50.5	15.8	.074	
	M1+	20	63.2	11.1		68.4	10.7		
Resection	GTR/No Residual	13	46.2	13.8	.169	61.5	13.5	.345	
	<GTR or Residual	3							
Histology	Unknown	14	78.6	11.0		85.7	9.4		
	Desmoplastic	18	50.5	11.8	.038	60.6	11.6	.046	
	Non-Desmoplastic	4							
	Unable to Determine	13	84.6	10.0					
Desmoplasia -M-Stage	Desmoplastic M0	10	60.0	15.5	.091				
	Non-Desmoplastic M0	1	0						
	Desmoplastic M1+	8	37.5	17.1	.014				
	Non-Desmoplastic M1+	4							
	Unable to Determine								