



Full Length Article

Pediatric

Effect of Autograft CD34⁺ Dose on Outcome in Pediatric Patients Undergoing Autologous Hematopoietic Stem Cell Transplant for Central Nervous System Tumors



Tristan E. Knight^{1,2}, Kwang Woo Ahn^{3,4}, Kyle M. Hebert⁴, Rasha Atshan⁴, Donna A. Wall⁵, Kanhatai Chiengthong^{6,7}, Seth J. Rotz⁸, Ellen Faint⁹, Hemalatha G. Rangarajan¹⁰, Jeffery J. Auletta^{11,12}, Akshay Sharma¹³, Carrie L. Kitko¹⁴, Hasan Hashem¹⁵, Kirsten M. Williams¹⁶, Baldeep Wirk¹⁷, Christopher C. Dvorak¹⁸, Kasiani C. Myers¹⁹, Michael A. Pulsipher²⁰, Anne B. Warwick²¹, Nahal Rose Lalefar²², Kirk R. Schultz²³, Muna Qayed¹⁶, Larisa Broglie^{4,24,*}, Mary Eapen⁴, Gregory A. Yanik²⁵

¹ Cancer and Blood Disorders Center, Seattle Children's Hospital, Seattle, Washington

² Division of Hematology and Oncology, Department of Pediatrics, University of Washington School of Medicine, Seattle, Washington

³ Division of Biostatistics, Institute for Health and Equity, Medical College of Wisconsin, Milwaukee, Wisconsin

⁴ CIBMTR® (Center for International Blood and Marrow Transplant Research), Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin

⁵ Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

⁶ Division of Pediatric Hematology and Oncology, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

⁷ King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand

⁸ Department of Pediatric Hematology, Oncology, and Blood and Marrow Transplantation, Cleveland Clinic, Cleveland, Ohio

⁹ Division of Pediatric Hematology, Oncology, and Cellular Therapy, The Children's Hospital at Montefiore, Bronx, New York

¹⁰ Department of Pediatric Hematology, Oncology, Blood and Marrow Transplantation, Nationwide Children's Hospital, Columbus, Ohio

¹¹ CIBMTR (Center for International Blood and Marrow Transplant Research), National Marrow Donor Program/Be The Match, Minneapolis, Minnesota

¹² Hematology/Oncology/BMT and Infectious Diseases, Nationwide Children's Hospital, Columbus, Ohio

¹³ Department of Bone Marrow Transplantation and Cellular Therapy, St. Jude Children's Research Hospital, Memphis, Tennessee

¹⁴ Division of Pediatric Hematology/Oncology, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee

¹⁵ Division of Pediatric Hematology/Oncology and Bone Marrow Transplantation, King Hussein Cancer Center, Amman, Jordan

¹⁶ Aflac Cancer and Blood Disorders Center, Emory University and Children's Healthcare of Atlanta, Atlanta, Georgia

¹⁷ Bone Marrow Transplant Program, Penn State Cancer Institute, Hershey, Pennsylvania

¹⁸ Division of Pediatric Allergy, Immunology & Bone Marrow Transplantation, Benioff Children's Hospital, University of California San Francisco, San Francisco, California

¹⁹ Department of Pediatrics, University of Cincinnati College of Medicine, Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

²⁰ Intermountain Primary Children's Hospital Division of Hematology and Oncology, Huntsman Cancer Institute at the Spencer Eccles Fox School of Medicine at the University of Utah, Salt Lake City, Utah

²¹ Department of Pediatrics, Uniformed Services University of the Health Sciences, Bethesda, Maryland

²² Division of Pediatric Hematology, UCSF Benioff Children's Hospital, Oakland, California

²³ Department of Pediatric Hematology, Oncology and Bone Marrow Transplant, British Columbia's Children's Hospital, The University of British Columbia, Vancouver, British Columbia, Canada

²⁴ Division of Pediatric Hematology/Oncology/Blood and Marrow Transplant, Department of Pediatrics, Medical College of Wisconsin, Milwaukee, Wisconsin

²⁵ Mott Children's Hospital, University of Michigan Medical Center, Ann Arbor, Michigan

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Consolidation with autologous hematopoietic stem cell transplantation (HSCT) has improved survival for patients with central nervous system tumors (CNSTs). The impact of the autologous graft CD34⁺ dose on patient outcomes is unknown. We wanted to analyze the relationship between CD34⁺ dose, total nucleated cell (TNC) dose, and clinical outcomes, including overall survival (OS), progression-free survival (PFS), relapse, non-relapse mortality (NRM), endothelial-injury complications (EIC), and time to neutrophil engraftment in children undergoing autologous HSCT for CNSTs. A retrospective analysis of the CIBMTR database was performed. Children aged <10 years

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*Correspondence and reprint requests: Larisa Broglie, Medical College of Wisconsin, 8701 Watertown Plank Rd, MFRC 3018, Milwaukee, WI 53226

E-mail address: lbrogli@mcw.edu (L. Broglie).

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Autologous hematopoietic stem
cell transplant
CD34+
Central nervous system
Medulloblastoma
TNC

who underwent autologous HSCT between 2008 to 2018 for an indication of CNST were included. An optimal cut point was identified for patient age, CD34⁺ cell dose, and TNC, using the maximum likelihood method and PFS as an endpoint. Univariable analysis for PFS, OS, and relapse was described using the Kaplan-Meier estimator. Cox models were fitted for PFS and OS outcomes. Cause-specific hazards models were fitted for relapse and NRM. One hundred fifteen patients met the inclusion criteria. A statistically significant association was identified between autograft CD34⁺ content and clinical outcomes. Children receiving $>3.6 \times 10^6/\text{kg}$ CD34⁺ cells experienced superior PFS ($p = .04$) and OS ($p = .04$) compared to children receiving $\leq 3.6 \times 10^6/\text{kg}$. Relapse rates were lower in patients receiving $>3.6 \times 10^6/\text{kg}$ CD34⁺ cells ($p = .05$). Higher CD34⁺ doses were not associated with increased NRM ($p = .59$). Stratification of CD34⁺ dose by quartile did not reveal any statistically significant differences between quartiles for 3-year PFS ($p = .66$), OS ($p = .29$), risk of relapse ($p = .57$), or EIC ($p = .87$). There were no significant differences in patient outcomes based on TNC, and those receiving a TNC $>4.4 \times 10^8/\text{kg}$ did not experience superior PFS ($p = .26$), superior OS ($p = .14$), reduced risk of relapse ($p = .37$), or reduced NRM ($p = .25$). Children with medulloblastoma had superior PFS ($p < .001$), OS ($p = .01$), and relapse rates ($p = .001$) compared to those with other CNS tumor types. Median time to neutrophil engraftment was 10 days versus 12 days in the highest and lowest infused CD34⁺ quartiles, respectively. For children undergoing autologous HSCT for CNSTs, increasing CD34⁺ cell dose was associated with significantly improved OS and PFS, and lower relapse rates, without increased NRM or EICs.

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Central nervous system tumors (CNSTs) are one of the most common indications for autologous hematopoietic stem cell transplantation (HSCT) in children [1]. Although many CNSTs are radiation-sensitive, radiotherapy may result in severe neurodevelopmental sequelae or secondary malignant neoplasms, with younger age at the time of irradiation being the greatest risk factor for these late effects [2–4]. Historically, radiation-sparing treatment strategies resulted in dismal outcomes, with 2- to 3-year progression-free survival (PFS) of 0% to 34%, and median time-to-relapse of 6 to 9 months [5–10]. Subsequent studies of children with relapsed/recurrent CNSTs were able to achieve event-free survival (EFS) rates approaching 50% via single autologous HSCTs [11–14], with this approach therefore being integrated into front-line clinical trials for newly diagnosed children, with continual improvements in patient outcomes across tumor types have been achieved via the use of consolidative autologous HSCTs [15–22]. Subsequent trials involving multiple sequential (e.g., tandem) have shown this to be a relatively safe and effective approach [23], with additional studies ongoing [24,25].

The impact of the infused autologous graft (autograft) on patient outcomes for children with CNSTs has not been well described to date. Data from adult patients with a range of solid tumor types has suggested that infusion of higher CD34⁺ doses results in shortened time to neutrophil engraftment, lessened need for supportive care [26,27], and improved survival [28,29]. However, autologous HSCTs are generally not performed for adults with CNSTs [30]. In addition, pediatric peripheral blood stem cell (PBSC) collections may contain 2 to 10 times higher levels of CD34⁺ cells than those of adults, potentially greatly exceeding the level necessary for hematopoietic recovery [31–36]. Selecting the optimal CD34⁺ cell dose for infusion would help guide the management of patients undergoing autologous transplantation for CNSTs.

Prior data have shown an association between higher CD34⁺ doses and a shortened time to hematopoietic recovery [26,27]. However, more rapid hematopoietic recovery may be associated with a heightened incidence of endothelial-injury related complications (EICs) [37–39]. Such complications, including engraftment syndrome, idiopathic pneumonia syndrome (IPS), transplantation-associated thrombotic microangiopathy, and veno-occlusive disease/sinusoidal obstructive syndrome (VOD/SOS), occur because of interactions between injured endothelial cells and activated immune effector cells [40,41] and are a major contributor to non-relapse mortality

(NRM) [41,42]. Large CD34⁺ doses could theoretically either improve or worsen outcomes, and the ideal CD34⁺ autograft content is not known for CNST. This analysis therefore assesses the relationship between CD34⁺ dose and clinical outcomes including progression-free survival, overall survival, relapse rates, non-relapse mortality, endothelial injury complications, and neutrophil engraftment in 115 children who underwent autologous transplantation for central nervous system tumors.

METHODS

Data Source

All data were obtained via the Center for International Blood and Marrow Transplant Research (CIBMTR) registry, which contains information on more than 575,000 individual patients, obtained from >350 distinct transplantation centers worldwide. All data are deidentified and reported on standardized forms, with participation being voluntary, and bias minimized via consecutive reporting requirements. Patients were eligible for inclusion if they underwent an autologous HSCT (either single or tandem) for CNST and were aged under 10 years of age at the time of transplantation. Additional inclusion criteria included transplantation occurring in Canada or the United States of America, between the years of 2008–2018 (inclusive). Patients were included if pretransplantation disease status was reported as complete response or partial response. Children receiving salvage HSCT after failure of primary therapy could not specifically be excluded, but the requirement of a pretransplantation disease status of complete response or partial response likely minimized the number of included patients with refractory disease. This study was approved by the National Marrow Donor Program's Institutional Review Board.

Patients

Children received treatment according to relevant cooperative group protocols, including Children's Cancer Group (CCG), Pediatric Oncology Group, Children's Oncology Group (COG), National Experimental Therapeutics Consortium, or St. Jude Children's Research Hospital protocols. The study enrollment/treatment protocol was not specifically recorded. Patients undergoing tandem transplantations were assessed on the basis of the CD34⁺ dose of the initial HSCT. If unavailable, the CD34⁺ dose of a subsequent HSCT was used, based on the assumption that CD34⁺ dose would be equal between transplant infusions.

Statistical Analysis

Progression-free survival was the primary study endpoint and was defined as alive and in remission. Secondary endpoints included overall survival, relapse rate, non-relapse mortality, incidence of endothelial injury, and time (in days) to neutrophil engraftment (defined as an absolute neutrophil count $\geq 0.5 \times 10^9/L$ for 3 or more consecutive days). The incidence of EICs was assessed as composite variable and included the occurrence of engraftment syndrome, IPS, VOD/SOS, thrombotic microangiopathy, and diffuse alveolar hemorrhage. Relapse was considered to be recurrence or progression of primary disease, and non-relapse mortality was considered to be death in the absence of disease recurrence or progression. Censure was performed at the time of last contact for surviving patients.

Cumulative incidence estimator with Gray's test was used to calculate the incidence of EICs, neutrophil engraftment, relapse, and NRM to accommodate competing risks. The Kaplan-Meier estimator, which estimates the probability of surviving as a function of time, was used to calculate OS (event defined as death from any cause) and PFS (event defined as relapse or death). A Cox model for PFS and OS and a cause-specific hazards model were constructed and included the following variables: sex, age at the time of transplantation, disease status before transplantation, single or tandem transplantation, infused TNC dose, and the infused dose of CD34⁺ cells. CD34⁺ and TNC dose cut-points were determined via the maximum likelihood method for PFS, and analyzed as a binary variable (e.g., over/under the cut-point). Stepwise selection was used to select significant variables, with those that achieve a *p* value $\leq .05$ or less being included in the final model; CD34⁺ cell dose was included in the final model irrespective of significance level attained. The *p* values ≤ 0.05 were considered statistically significant. No first-order interactions were observed between CD34⁺ cell dose and the other variables in the final model. Adjusted survival and cumulative incidence curves were created based on the final regression model [43,44]. All analyses were performed via SAS version 9.4 (Cary, NC).

RESULTS

Patient Characteristics

One hundred fifteen patients were eligible. Patient demographics and HSCT details (including conditioning regimens and EIC incidence) are displayed in Table 1. Median age at the time of HSCT was 3 years (range <1 to 10 years). Seventy-six (66%) of children had a complete response, with the remaining 39 (34%) having a partial response before HSCT. Tandem HSCT was performed in 81 (70%) of patients, and single HSCT in 29 (25%). Data regarding number of transplants was unavailable in 5 (4%) children. Sixty-five (57%) children had a diagnosis of medulloblastoma. The median length of follow-up for the study population was 67 months (range 9–132 months). All (100%) included patients used autologous peripheral blood stem cells as the graft source.

Effect of CD34⁺ Cell Dose

Autografts contained a median CD34⁺ of $4.7 \times 10^6/kg$ (range 0.5–66.9 $\times 10^6/kg$) (Table 1). The study population was also examined based on CD34⁺ dose quartiles, with the interquartile range being 2.7–8.3 $\times 10^6/kg$ (Table 1). Demographic characteristics were similar across CD34⁺ dose quartiles.

Optimal CD34⁺ dose

A CD34⁺ dose of $3.6 \times 10^6/kg$ was identified as the optimal cell dose “cut point” to discriminate between the largest

differences in outcome (Table 2). Autografts which contained $>3.6 \times 10^6/kg$ were associated with significantly superior PFS (hazard ratio [HR] = 0.55; 95% confidence interval [CI], 0.31–0.97; *p* = .04; Figure 1), superior OS (HR = 0.49; 95% CI, 0.25–0.98; *p* = .04; Figure 2), and lower relapse rate (HR = 0.56; 95% CI, 0.31–1.01; *p* = .05; Figure 3). No association was identified between CD34⁺ cell dose and NRM (HR = 0.46; 95% CI, 0.03–7.48; *p* = .59). EIC incidence was not associated with CD34⁺ dose at 100 days, 6 months, and 1 year after transplantation (*p* = .91; Table 3).

Interquartile Difference in Outcome

The association between clinical outcomes and CD34⁺ cell dose was also analyzed by quartiles (Supplementary Table S1). No quartile was associated with a statistically superior outcome for PFS (*p* = .66; Figure 4), OS (*p* = .29; Figure 5), or relapse rate (*p* = .57; Figure 6) at 1 or 3 years after transplantation. EIC incidence did not vary significantly according to CD34⁺ dose quartile at 100 days, 6 months, or 1 year after transplantation (*p* = .87; Table 4). Descriptive statistics were calculated for patients who received low (e.g., $\leq 2 \times 10^6/kg$) (*n* = 18) or high (e.g., $\geq 10 \times 10^6/kg$) (*n* = 20) CD34⁺ cell doses. Among children receiving $\leq 2 \times 10^6/kg$ CD34⁺ cells, the 3-year PFS and OS were 55.6% and 77.8%, respectively. Children who received $\geq 10 \times 10^6/kg$ CD34⁺ cells experienced similar outcomes, with 3-year PFS and OS of 65% and 80%, respectively. Three-year relapse rates were 8/18 (44.4%) children who received doses $\leq 2 \times 10^6/kg$ relapsed, versus 7/20 (35%) who received $\geq 10 \times 10^6/kg$ CD34⁺ cells.

Endothelial Injury Complications

Six of the 115 patients (5%) developed EICs, including 5 who experienced IPS, and 1 who experienced VOD/SOS. Among the 6 patients, 3 received conditioning with carboplatin/cyclophosphamide/vincristine, and 3 received conditioning with carboplatin/thiotepa. The median infused CD34⁺ cell dose among children who developed EICs was $4.2 \times 10^6/kg$ (range 1.36–8.74), and the median infused TNC dose was $3.1 \times 10^8/kg$ (range 0.54–5.44). From the available data, it was not possible to determine whether EICs arose after the first or subsequent HSCT or whether EICs occurred more frequently after first versus subsequent HSCTs.

Neutrophil Engraftment

Neutrophil engraftment occurred in 114/115 (99.1%) children by day 28 after HSCT, with the median time to engraftment being 10 to 12 days across all CD34⁺ dose quartiles (Table 5). No specific CD34⁺ dose was found to predict more rapid neutrophil engraftment. The median time to engraft neutrophils was 12 days (range 11–13 days) in the lowest dose quartile compared to 10 days (range 9–11 days) for the highest quartile. All 17 evaluable patients who received a cell dose of $\leq 2 \times 10^6/kg$ engrafted, with a median time-to-neutrophil recovery of 11 days (range 10–12 days). Nineteen of 20 patients (95%) who received a cell dose $\geq 10 \times 10^6/kg$ had neutrophil recovery by day 28, the median time to neutrophil engraftment = 10 days. Data regarding neutrophil recovery after second HSCTs (when performed) were not available.

Effect of TNC Dose

The median TNC was $2.4 \times 10^8/kg$ (range 0.4–49.8 $\times 10^8/kg$), with an interquartile range of 1.3–5.7 $\times 10^8/kg$ (Table 1). A TNC dose of $4.4 \times 10^8/kg$ was identified as the optimal cell dose “cut point” to discriminate between the largest differences in outcome. However, there was no significant difference

Table 1
Characteristics of Patients Undergoing Autologous HSCT for Central Nervous System Tumors

	Study Population	CD34 ⁺ Dose by Quartile (× 10 ⁶ /kg)			
		0.49 - 2.70	2.71 - 4.66	4.67 - 8.25	8.26 - 66.94
No. of patients	115 (100%)	29 (25.2%)	28 (24.3%)	29 (25.2%)	29 (25.2%)
Age at transplantation (yr)					
Median (min-max)	3 (1-10)	5 (1-9)	5 (1-10)	2 (1-8)	3 (1-7)
Less than 1	6 (5%)	1 (3%)	1 (4%)	3 (10%)	1 (3%)
1 to 2	42 (37%)	8 (28%)	4 (14%)	13 (45%)	17 (59%)
3 to 5	40 (35%)	8 (28%)	12 (43%)	10 (34%)	10 (34%)
6 to 9	27 (23%)	12 (41%)	11 (39%)	3 (10%)	1 (3%)
Sex					
Male	74 (64%)	21 (72%)	13 (46%)	23 (79%)	17 (59%)
Female	41 (36%)	8 (28%)	15 (54%)	6 (21%)	12 (41%)
CNS tumor type, no. (%)					
Medulloblastoma	65 (57%)	16 (55%)	20 (71%)	15 (52%)	14 (48%)
Other CNS tumors*	50 (43%)	13 (45%)	8 (29%)	14 (48%)	15 (52%)
Disease status before transplantation					
Complete response	59 (51%)	11 (38%)	17 (61%)	13 (45%)	18 (62%)
Complete response—undetermined	17 (15%)	7 (24%)	2 (7%)	7 (24%)	1 (3%)
Partial response	39 (34%)	11 (38%)	9 (32%)	9 (31%)	10 (34%)
Transplant type					
Single HSCT	29 (25%)	4 (14%)	10 (36%)	6 (21%)	9 (31%)
Tandem HSCT	81 (70%)	24 (83%)	18 (64%)	21 (72%)	18 (62%)
Not reported	5 (4%)	1 (3%)	0 (0%)	2 (7%)	2 (7%)
CD34 ⁺ dose, cells × 10 ⁶ /kg					
Median (min-max)	4.7 (0.5 – 66.9)	1.7 (0.5-2.7)	3.7 (2.8-4.5)	6.0 (4.7-8.1)	12.1 (8.3-66.9)
Interquartile range	2.7 – 8.3	0.9-2.4	3.2-4.0	5.0-6.7	9.6-17.5
Total nucleated cell dose, cells × 10 ⁸ /kg					
Median (min-max)	2.4 (0.4 – 49.8)	3.8 (0.4-48.4)	5.1 (0.8-47.6)	1.4 (0.4-49.8)	2.2 (0.8-13.4)
Inter-quartile range	1.3 – 5.7	2.2-6.5	1.9-9.7	0.9-3.2	1.4-5.5
Follow-up (mo), median (min-max)	67 (9-132)	54 (9-124)	73 (11-132)	74 (12-144)	76 (23-124)
Conditioning regimen of first transplantation					
Cyclophosphamide/Fludarabine	1 (1%)				
Carboplatin/Etoposide	27 (23%)				
Carboplatin/Thiotepa	59 (51%)				
Carboplatin	3 (3%)				
Carboplatin/Cyclophosphamide/Vincristine ± Amifostine	23 (20%)				
Etoposide/Thiotepa	1 (1%)				
None	1 (1%)				

* Other CNS tumors: Rhabdoid tumors (n=14), Pineoblastoma (n=10), Anaplastic astrocytoma (n=3), Cerebral neuroblastoma (n=2), Anaplastic ependymoma (n=1), Ependymoblastoma (n=1), Glioblastoma multiforme (n=1), Primary brain sarcomas (n=1), Other primitive neuroectodermal tumors (n=13), Other high grade glial tumors (n=2), Not reported (n=1).

in patient outcomes based on TNC, because patients who received autografts containing a TNC content $>4.4 \times 10^8$ /kg did not have significantly different outcomes from those patients who received autografts containing $\leq 4.4 \times 10^8$ TNC/kg. Specifically, a TNC $>4.4 \times 10^8$ /kg did not result in superior PFS ($p = .26$), superior OS ($p = .14$), reduced risk of relapse ($p = .37$), or reduced NRM ($p = .25$).

Overall Outcomes and Effects of Tumor Type and Tandem Transplantation

Patient outcomes including PFS, OS, Relapse, NRM, and EIC incidence are displayed in Table 6. Three-year PFS was 58.6% (95% CI, 49.4%-67.8%) for the study population, and 3-year OS was 75.5% (95% CI, 67.4%-83.6%). Children with diagnoses other than medulloblastomas experienced worse outcomes than those with medulloblastomas, including lower PFS

(HR = 2.87; 95% CI, 1.69-5.15; $p < .001$), lower OS (HR = 2.59; 95% CI, 1.28-5.25; $p = .01$), and a higher risk of relapse (HR = 2.67; 95% CI, 1.58-4.82; $p = .001$) (Table 2).

We assessed for any difference in outcomes based on the number of transplantations performed and identified no statistically significant change in outcome between patients who had undergone single versus tandem transplantation. Those who underwent tandem HSCT did not have demonstrable improvements PFS (HR = 0.74; 95% CI, 0.39-1.41; $p = .36$), OS (HR = 1.03; 95% CI, 0.46-2.29; $p = .94$), or risk of relapse (HR = 0.69; 95% CI, 0.36-1.34; $p = .27$), compared to those who underwent single HSCT (Supplementary Table S2).

DISCUSSION

In a retrospective analysis of 115 children undergoing autologous HSCT for central nervous system tumors, higher

Table 2
Multivariable Analysis – Outcomes

	N	HR	95% CI Lower Limit	95% CI Upper Limit	p Value
Progression-free survival					
CD34 ⁺ dose ($\times 10^6$ /kg)					.04
≤3.6	42	1			
>3.6	71*	0.55	0.31	0.97	
CNS type					<.001
Medulloblastoma	64	1			
Other CNS tumors	49	2.87	1.60	5.15	
Overall Survival					
CD34 ⁺ dose ($\times 10^6$ /kg)					.04
≤3.6	42	1			
>3.6	73	0.49	0.25	0.98	
CNS type					.01
Medulloblastoma	65	1			
Other CNS tumors	50	2.59	1.28	5.25	
Relapse					
CD34 ⁺ dose ($\times 10^6$ /kg)					.05
≤3.6	42	1			
>3.6	71*	0.56	0.31	1.01	
CNS type					.001
Medulloblastoma	64	1			
Other CNS tumors	49	2.67	1.48	4.82	
Non-relapse mortality					
CD34 ⁺ dose ($\times 10^6$ /kg)					.59
≤3.6	42	1			
>3.6	71*	0.46	0.03	7.48	

* Progression-free survival, relapse, and non-relapse mortality data were not available for 2 patients.

CD34⁺ doses were associated with significantly improved PFS and OS, and a lessened risk of relapse. Specifically, patients who received greater than 3.6×10^6 /kg had superior outcomes compared to those receiving lower doses, and the administration of higher CD34⁺ cell doses did not result in increased NRM or EIC.

This is one of the first studies in pediatric stem cell transplantation to show such associations. In contrast, the impact of the autograft CD34⁺ cell dose on outcomes has been well described in a number of adult studies, with variable results [28,29,45]. Several adult studies have not shown a correlation between CD34⁺ dose and outcome [45], whereas others have shown an association between higher CD34⁺ doses and improved PFS and OS [28,29]. Additionally, adult data have suggested that CD34⁺ doses $<2 \times 10^6$ /kg may delay

hematopoietic recovery [46,47], whereas autograft cell doses $>5 \times 10^6$ /kg CD34⁺ may be associated with more rapid engraftment [26,27]. Compared to adult autograft trials, CD34⁺ cell doses are typically much larger in the pediatric population [29,45]. Thus pediatric-specific data are therefore needed.

One rationale for conducting our current study was to assess whether higher CD34⁺ cell doses were associated with an increased NRM and EIC, given the potential interaction between immune effector cells and endothelial cells in the transplantation process [40,41]. In our current trial, we did not identify any association between EIC incidence, NRM, and CD34⁺ dose.

Given that CD34⁺ cells make up approximately 1% to 3% of the autologous graft [48], the impact of TNC content on HSCT outcomes was also examined in our trial. The majority of cells

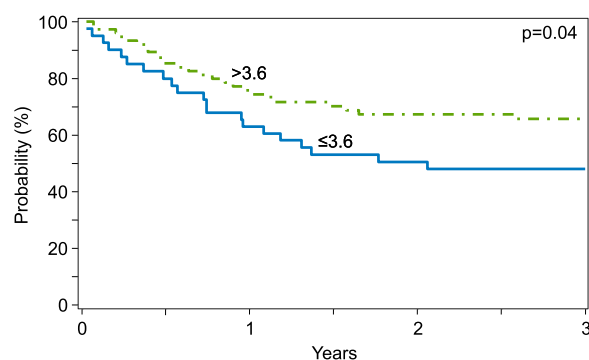


Figure 1. Progression-free survival by CD34⁺ dose ($\times 10^6$ /kg).

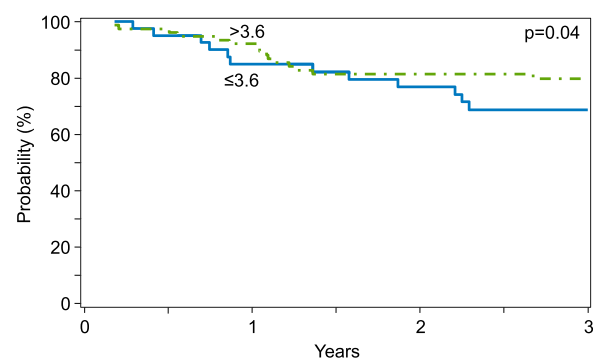


Figure 2. Overall survival by CD34⁺ dose ($\times 10^6$ /kg).

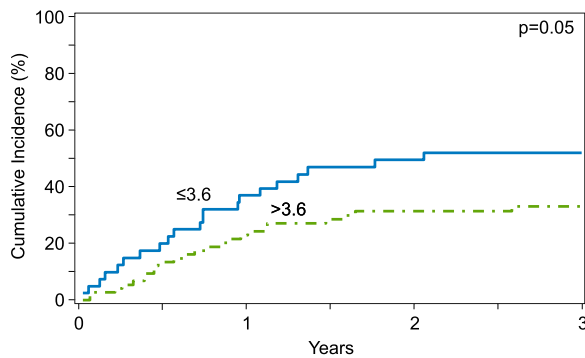


Figure 3. Relapse rate by CD34⁺ dose ($\times 10^6/\text{kg}$).

in a typical autograft are a heterogeneous mixture of lineage-differentiated progenitors and immune effector cells (IECs) [49–51]. Although we did not observe differences in outcome based on infused TNC, we lacked the ability to investigate specific sub-mononuclear cell populations within the graft. Future prospective investigations into this area are warranted, however, because the importance of IECs in disease control is being increasingly understood. Promising clinical trials have investigated the use of directly modify T cells and NK cells to facilitate tumor targeting [52,53]. Congruently, there is expanding use of antitumor vaccines, immune checkpoint inhibition, and oncolytic viral therapies, all of which rely to some extent on the patient's own immunologic response, as mediated by endogenous unmodified IECs [52,53]. Granular investigations into autologous graft IEC content may therefore yield actionable data as these clinical trials continue to grow in number and efficacy.

The observed OS and PFS compared favorably to other autograft studies in children with CNSTs. CCG 99703 used a triple tandem HSCT approach to treat children with embryonal CNSTs, with a 5-year OS of $63.6\% \pm 5\%$ and 5-year EFS of $43.9\% \pm 5.2\%$ [23]. HeadStart I reported 2-year OS and EFS of $55\% \pm 6\%$ and $39\% \pm 7\%$, respectively [15]. HeadStart II reported 3-year OS and EFS rates of 60% and 49% [16–18], with HeadStart III noting 5-year OS and EFS rates of $62\% \pm 5\%$ and $46\% \pm 5\%$, respectively, for patients with medulloblastoma [21]. In general, patients with medulloblastoma have experienced superior outcomes on these trials, compared to patients with other diagnoses [16–18]. Results for the current clinical trials COG ACNS0334 and HeadStart IV are not yet available. Several features of our study may explain the superior outcomes we observed. First, only patients who underwent auto-HSCT were included, with the effect of excluding patients with the most advanced/aggressive CNSTs. Patients who died, had progressive disease, or were otherwise ineligible for transplantation were therefore not represented in our results. Second, the study window encompassed only transplantations performed from 2008 to 2018. The results of the National Experimental Therapeutics Consortium's HeadStart I and II clinical trials had been published by early 2008 [17,18], HeadStart III closed to

Table 3
EIC Incidence by Optimal CD34⁺ Dose ($p = .91$)

	$\leq 3.6 \times 10^6/\text{kg}$ (N = 42)	$> 3.6 \times 10^6/\text{kg}$ (N = 71)*
100 day	0%	4.1% (95% CI = 0.8%–9.9%)
6 months	2.5% (95% CI = 0%–9.6%)	4.1% (95% CI = 0.8%–9.9%)
1 year	5% (95% CI = 0.5%–13.9%)	4.1% (95% CI = 0.8%–9.9%)

* Data unavailable for 2 patients

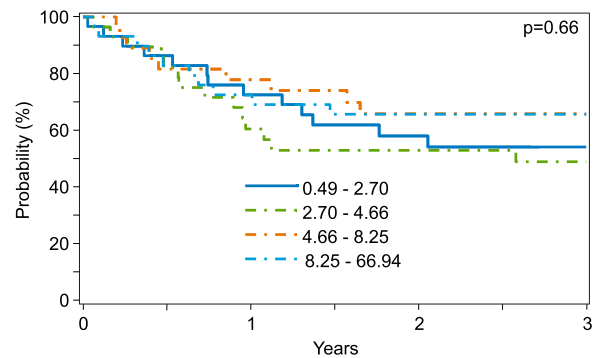


Figure 4. Progression-free survival by CD34⁺ dose quartile ($\times 10^6/\text{kg}$).

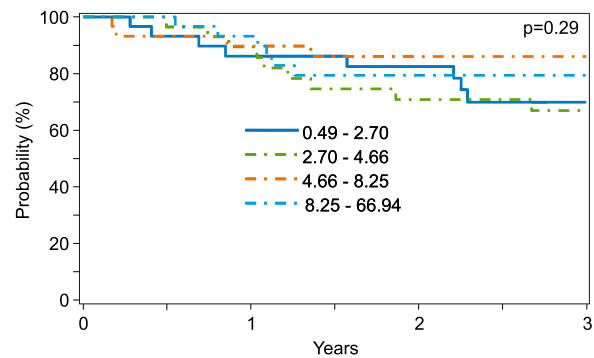


Figure 5. Overall survival by CD34⁺ dose quartile ($\times 10^6/\text{kg}$).

accrual in December 2009, and HeadStart IV opened to accrual in September 2015 [24]. The COG's ACNS0334 clinical trial likewise opened to accrual in October 2007 and closed in December 2016 [25]. We therefore examined a population of patients who likely benefited from recent progress in CNST treatment and received therapy according to current multicenter trials, because 70% of participants in our study received tandem HSCTs. Last, patients > 10 years of age were excluded because differences in disease biology, management strategies, and the prognosis in this older population [54,55]. The observed NRM in our study likewise compared favorably to other pediatric CNST transplantation studies. The day 100 NRM for the HeadStart I, II, and III trials were 6.4% ($n = 3$), 2.1% ($n = 1$), and 0.8% ($n = 1$), respectively [5]. CCG-99703 reported a “toxic mortality rate” of 2.5% ($n = 2$), attributed to the auto-HSCTs performed in that study [23].

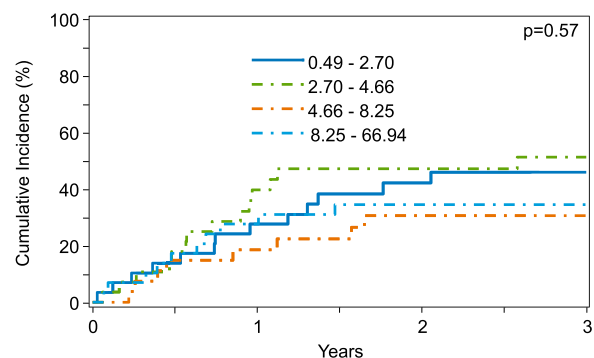


Figure 6. Relapse rate by CD34⁺ dose quartile ($\times 10^6/\text{kg}$).

Table 4EIC Incidence by CD34+ Dose Quartiles ($\times 10^6/\text{kg}$) ($p = .87$)

	Probability of EIC (95% CI)			
	0.49–2.70 (N = 28)	2.71–4.66 (N = 28)	4.67–8.25 (N = 29)	8.26–66.94 (N = 28)
100 days	0%	0%	6.9% (0.6–19)	3.6% (0–13.7)
6 months	3.6% (0–13.7)	0%	6.9% (0.6–19)	3.6% (0–13.7)
1 year	7.1% (0.7–19.7)	0%	6.9% (0.6–19)	3.6% (0–13.7)

Table 5

Time to Neutrophil Engraftment by CD34+ Dose Quartiles

	Days to neutrophil engraftment			
	0.49–2.70 $\times 10^6/\text{kg}$ (N = 28)	2.71–4.66 $\times 10^6/\text{kg}$ (N = 28)	4.67–8.25 $\times 10^6/\text{kg}$ (N = 29)	8.26–66.94 $\times 10^6/\text{kg}$ (N = 28)
Median (min–max)	12 (1–16)	10 (1–22)	11 (9–19)	10 (9–22)
5th–95th percentile	1–16	4–15	10–13	9–14
25th–75th percentile	11–13	10–12	10–12	9–11

No difference in outcomes was seen based on whether patients received single versus tandem transplantations. However, existing studies would suggest the superiority of tandem transplantation in the CNS tumor setting [23–25]. Although this may therefore be a surprising observation, the goal of this investigation was not to assess for the effect of transplant number. Neither study methodology nor sample size was optimized for this endpoint. It can therefore only be reported that the observed associations between CD34+ cell dose and patient outcomes was not influenced by the number of transplantations performed.

Our study has a number of limitations. First, we were necessarily limited to data fields included by the CIBMTR, which do not capture the induction regimen used, number of cycles of pre-apheresis or pre-transplant chemotherapy, and presence/absence of marrow disease at the time of diagnosis, transplantation, or apheresis. We are therefore unable to assess the impact of specific treatment protocols on outcomes. We were also unable to analyze for an association between CD34+ dose and platelet recovery or hospitalization length, because these data were not captured [56,57]. Second, our

findings may have been confounded by pretransplantation disease burden or treatment response, because these data were not specifically captured. Patients with greater disease burden may have been less able to mobilize CD34+ cells and therefore both collected and received lower CD34+ doses. Conversely, patients receiving higher CD34+ doses may have been those whose disease was less severe. This effect has been seen in adult patients with lymphoma [58,59], but it is unclear whether it applies to children with CNSTs. We sought to minimize the influence of this by including only patients who had partial or complete responses to therapy, but patient disease status may still have influenced our observed results. We also assessed the cohort of patients who received CD34+ cell doses $\leq 2.0 \times 10^6/\text{kg}$. Although the small size of this group precluded valid statistical modeling, these children did not have notably poorer outcomes based on descriptive statistics alone. Third, our population was heterogeneous and included patients with a variety of different CNSTs. The observed effect of CD34+ dose was independent of diagnosis, but disease-specific subset analysis may have resulted in different outcomes for the different types of CNSTs. Because of the relatively small number of patients with any specific, non-medulloblastoma diagnosis, we did not perform such an analysis.

In conclusion, we identified an association between higher autograft CD34+ content and superior PFS and OS, and lower relapse rates. There was no association between CD34+ dose and the occurrence of NRM or EIC. The effect of CD34+ cell dose upon patient outcomes suggests that there may be sufficient grounds to investigate whether a higher CD34+ target might yield improved outcomes in pediatric patients with CNSTs.

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Table 6

Patient Outcomes

Outcomes	CNS Tumors (N = 115)	
	N	% Prob (95% CI)
Progression-free survival	113	
1-year		70.8% (62.1–78.8)
3-year		58.6% (49.4–67.8)
Overall survival	115	
1-year		89.5% (83.3–94.4)
3-year		75.5% (67.4–83.6)
Relapse	113	
1-year		28.4% (20.4–37)
3-year		40.5% (31.3–49.8)
Non-relapse mortality	114	
1-year		0.9% (0–3.5)
3-year		0.9% (0–3.5)
Endothelial injury complications*	115	
100-day		4.3% (1.4–8.8)
1-year		6.1% (2.5–11.2)

* Endothelial injury complications is a composite endpoint consisting of time to first of the following events: engraftment syndrome, IPS, VOD/SOS, thrombotic microangiopathy, or diffuse alveolar hemorrhage.

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Authorship statement: TEK was responsible for designing and writing the study protocol, analyzing data and interpreting results, and writing and editing the manuscript. KWA, KMH, and RA assisted in study protocol design, analyzed the data, designed and created study tables and figures and provided statistical analysis and support. DAW and KC assisted in

study protocol design and critically reviewed the manuscript and provided formative commentary. SJR, EF, HGR, JJA, AS, CLK, HH, KMW, BW, CCD, KCM, MAP, ABW, NRL, KRS, MQ, LB, ME, GAY critically reviewed the manuscript and provided formative commentary at the protocol, results, and manuscript writing stage. KRS and MQ assisted in interpretation of results, critically reviewed the manuscript, and provided formative commentary. LB, ME and GAY assisted in protocol design, analyzing data and interpreting results, and writing and editing the manuscript, and provided formative commentary.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2023.03.024.

REFERENCES

1. Khandelwal P, Millard HR, Thiel E, et al. Hematopoietic stem cell transplantation activity in pediatric cancer between 2008 and 2014 in the United States: a Center for International Blood and Marrow Transplant Research Report. *Biol Blood Marrow Transplant*. 2017;23:1342–1349.
2. Donahue B. Short- and long-term complications of radiation therapy for pediatric brain tumors. *Pediatr Neurosurg*. 1992;18:207–217.
3. Devarahally SR, Severson RK, Chuba P, Thomas R, Bhambhani K, Hamre MR. Second malignant neoplasms after primary central nervous system malignancies of childhood and adolescence. *Pediatr Hematol Oncol*. 2003;20:617–625.
4. Palmer SL, Goloubeva O, Reddick WE, et al. Patterns of intellectual development among survivors of pediatric medulloblastoma: a longitudinal analysis. *J Clin Oncol*. 2001;19:2302–2308.
5. Altshuler C, Haley K, Dhall G, et al. Decreased morbidity and mortality of autologous hematopoietic transplants for children with malignant central nervous system tumors: the “Head Start” trials, 1991–2009. *Bone Marrow Transplant*. 2016;51:945–948.
6. Geyer JR, Finlay JL, Boyett JM, et al. Survival of infants with malignant astrocytomas. A Report from the Children's Cancer Group. *Cancer*. 1995;75:1045–1050.
7. Geyer JR, Zeltzer PM, Boyett JM, et al. Survival of infants with primitive neuroectodermal tumors or malignant ependymomas of the CNS treated with eight drugs in 1 day: a report from the Children's Cancer Group. *J Clin Oncol*. 1994;12:1607–1615.
8. Geyer JR, Spoto R, Jennings M, et al. Multiagent chemotherapy and deferred radiotherapy in infants with malignant brain tumors: a report from the Children's Cancer Group. *J Clin Oncol*. 2005;23:7621–7631.
9. Grill J, Sainte-Rose C, Juvet A, et al. Treatment of medulloblastoma with postoperative chemotherapy alone: an SFOP prospective trial in young children. *Lancet Oncol*. 2005;6:573–580.
10. Duffner PK, Horowitz ME, Krischer JP, et al. Postoperative chemotherapy and delayed radiation in children less than three years of age with malignant brain tumors. *N Engl J Med*. 1993;328:1725–1731.
11. Finlay JL, Goldman S, Wong MC, et al. Pilot study of high-dose thiopeta and etoposide with autologous bone marrow rescue in children and young adults with recurrent CNS tumors. The Children's Cancer Group. *J Clin Oncol*. 1996;14:2495–2503.
12. Dunkel IJ, Gardner SL, Garvin JH, Goldman S, Shi W, Finlay JL. High-dose carboplatin, thiopeta, and etoposide with autologous stem cell rescue for patients with previously irradiated recurrent medulloblastoma. *Neuro-Oncol*. 2010;12:297–303.
13. Broniscer A, Nicolaides TP, Dunkel IJ, et al. High-dose chemotherapy with autologous stem-cell rescue in the treatment of patients with recurrent non-cerebellar primitive neuroectodermal tumors. *Pediatr Blood Cancer*. 2004;42:261–267.
14. Dupuis-Girod S, Hartmann O, Benhamou E, et al. Will high dose chemotherapy followed by autologous bone marrow transplantation supplant cranio-spinal irradiation in young children treated for medulloblastoma? *J Neurooncol*. 1996;27:87–98.
15. Mason WP, Grovas A, Halpern S, et al. Intensive chemotherapy and bone marrow rescue for young children with newly diagnosed malignant brain tumors. *J Clin Oncol*. 1998;16:210–221.
16. Chi SN, Gardner SL, Levy AS, et al. Feasibility and response to induction chemotherapy intensified with high-dose methotrexate for young children with newly diagnosed high-risk disseminated medulloblastoma. *J Clin Oncol*. 2004;22:4881–4887.
17. Fangusaro J, Finlay J, Spoto R, et al. Intensive chemotherapy followed by consolidative myeloablative chemotherapy with autologous hematopoietic cell rescue (AuHCR) in young children with newly diagnosed supratentorial primitive neuroectodermal tumors (sPNETs): report of the Head Start I and II experience. *Pediatr Blood Cancer*. 2008;50:312–318.

18. Dhall G, Grodman H, Ji L, et al. Outcome of children less than three years old at diagnosis with non-metastatic medulloblastoma treated with chemotherapy on the "Head Start" I and II protocols. *Pediatr Blood Cancer*. 2008;50:1169–1175.
19. Gardner SL, Asgharzadeh S, Green A, Horn B, McCowage G, Finlay J. Intensive induction chemotherapy followed by high dose chemotherapy with autologous hematopoietic progenitor cell rescue in young children newly diagnosed with central nervous system atypical teratoid rhabdoid tumors. *Pediatr Blood Cancer*. 2008;51:235–240.
20. Zaky W, Dhall G, Ji L, et al. Intensive induction chemotherapy followed by myeloablative chemotherapy with autologous hematopoietic progenitor cell rescue for young children newly-diagnosed with central nervous system atypical teratoid/rhabdoid tumors: the Head Start III experience. *Pediatr Blood Cancer*. 2014;61:95–101.
21. Dhall G, O'Neil SH, Ji L, et al. Excellent outcome of young children with nodular desmoplastic medulloblastoma treated on "Head Start" III: a multi-institutional, prospective clinical trial. *Neuro-Oncol*. 2020;22:1862–1872.
22. Venkatramani R, Ji L, Lasky J, et al. Outcome of infants and young children with newly diagnosed ependymoma treated on the "Head Start" III prospective clinical trial. *J Neurooncol*. 2013;113:285–291.
23. Cohen BH, Geyer JR, Miller DC, et al. 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. *Pediatr Neurol*. 2015;53:31–46.
24. Nationwide Children's Hospital. HeadStart4: newly diagnosed children (<10 y/o) with medulloblastoma and other CNS embryonal tumors clinical and molecular risk-tailored intensive and compressed induction chemotherapy followed by consolidation with randomization to either single cycle or to three tandem cycles of marrow-ablative chemotherapy with autologous hematopoietic progenitor cell rescue. Available at: <https://clinicaltrials.gov/ct2/show/NCT02875314>. Accessed May 20, 2021.
25. Children's Oncology Group. A Phase III randomized trial for the treatment of newly diagnosed supratentorial PNET and high risk medulloblastoma in children <36 months old with intensive induction chemotherapy with methotrexate followed by consolidation with stem cell rescue versus the same therapy without methotrexate. Available at <https://clinicaltrials.gov/ct2/show/NCT00336024>. Accessed May 23, 2021.
26. Schulman KA, Birch R, Zhen B, Pania N, Weaver CH. Effect of CD34(+) cell dose on resource utilization in patients after high-dose chemotherapy with peripheral-blood stem-cell support. *J Clin Oncol*. 1999;17(4):1227.
27. Hyder MA, Goebel WS, Ervin KD, et al. Low CD34(+) cell doses are associated with increased cost and worse outcome after tandem autologous stem cell transplantation in patients with relapsed or refractory germ cell tumors. *Biol Blood Marrow Transplant*. 2018;24:1497–1504.
28. Carlsten M, Jädersten M, Hellström A, et al. The Karolinska experience of autologous stem-cell transplantation for lymphoma: a population-based study of all 433 patients 1994–2016. *Exp Hematol Oncol*. 2019;8:7.
29. Turunen A, Valtola J, Partanen A, et al. Autograft cellular composition and outcome in NHL patients: results of the prospective multicenter GOA study. *Leuk Lymphoma*. 2020;61:2082–2092.
30. Kim MS, Cai J, Maniar A, Kartika T, Haslam A, Prasad V. Comparison of classification of indications for allogeneic and autologous transplant for adults in ASTCT Guidelines and evidence available in published literature. *JAMA Intern Med*. 2022;182:76–78.
31. Karow A, Wilhelm A, Ammann RA, et al. Peripheral blood progenitor cell collection in pediatric patients optimized by high pre-apheresis count of circulating CD34+ cells and high blood flow. *Bone Marrow Transplant*. 2019;54:885–893.
32. Tiwari AK, Pandey P, Subbaraman H, et al. Autologous peripheral blood stem cell harvest: Collection efficiency and factors affecting it. *Asian J Transfus Sci*. 2016;10:93–97.
33. Rhodes B, Anderlini P. Allogeneic peripheral blood stem cell collection as of 2008. *Transfus Apher Sci*. 2008;38:219–227.
34. Cesaro S, Tintori V, Nesi F, et al. A prospective study on the efficacy of mobilization of autologous peripheral stem cells in pediatric oncology patients. *Transfusion*. 2013;53:1501–1509.
35. Bojanic I, Mazic S, Rajic L, Jakovljevic G, Stepan J, Cepulic BG. Large volume leukapheresis is efficient and safe even in small children up to 15 kg body weight. *Blood Transfus*. 2017;15:85–92.
36. Veljkovic D, Vujic D, Nonkovic OS, Jevtic D, Zecevic Z, Lazic E. Mobilization and harvesting of peripheral blood stem cells in pediatric patients with solid tumors. *Ther Apher Dial*. 2011;15:579–586.
37. Schmid I, Stachel D, Pagel P, Albert MH. Incidence, predisposing factors, and outcome of engraftment syndrome in pediatric allogeneic stem cell transplant recipients. *Biol Blood Marrow Transplant*. 2008;14:438–444.
38. Ravoet C, Feremans W, Husson B, et al. Clinical evidence for an engraftment syndrome associated with early and steep neutrophil recovery after autologous blood stem cell transplantation. *Bone Marrow Transplant*. 1996;18:943–947.
39. Spitzer TR. Engraftment syndrome: double-edged sword of hematopoietic cell transplants. *Bone Marrow Transplant*. 2015;50:469–475.
40. Dvorak CC, Higham C, Shimano KA. Transplant-associated thrombotic microangiopathy in pediatric hematopoietic cell transplant recipients: a practical approach to diagnosis and management. *Front Pediatr*. 2019;7:133.
41. Palomo M, Diaz-Ricart M, Carbo C, et al. Endothelial dysfunction after hematopoietic stem cell transplantation: role of the conditioning regimen and the type of transplantation. *Biol Blood Marrow Transplant*. 2010;16:985–993.
42. Carreras E, Diaz-Ricart M. The role of the endothelium in the short-term complications of hematopoietic SCT. *Bone Marrow Transplant*. 2011;46:1495–1502.
43. Zhang X, Loberiza FR, Klein JP, Zhang MJ. A SAS macro for estimation of direct adjusted survival curves based on a stratified Cox regression model. *Comput Methods Programs Biomed*. 2007;88:95–101.
44. Zhang X, Zhang MJ. SAS macros for estimation of direct adjusted cumulative incidence curves under proportional subdistribution hazards models. *Comput Methods Programs Biomed*. 2011;101:87–93.
45. Sorigie M, Sancho JM, Morgades M, et al. Relapse risk after autologous stem cell transplantation in patients with lymphoma based on CD34+ cell dose. *Leuk Lymphoma*. 2017;58:916–922.
46. Bender JG, To LB, Williams S, Schwartzberg LS. Defining a therapeutic dose of peripheral blood stem cells. *J Hematother*. 1992;1:329–341.
47. Bai Y, Yao L, Wei T, et al. Presumed asymptomatic carrier transmission of COVID-19. *JAMA*. 2020;323:1406–1407.
48. Partanen A, Turunen A, Valtola J, et al. Mobilization characteristics, blood graft composition, and outcome in diffuse large B-cell lymphoma after autologous stem cell transplantation: Results from the prospective multicenter GOA study. *Transfusion*. 2021;61:516–525.
49. Porrata LF, Burgstaler EA, Winters JL, et al. Immunologic autograft engineering and survival in non-Hodgkin lymphoma. *Biol Blood Marrow Transplant*. 2016;22:1017–1023.
50. Porrata LF, Inwards DJ, Ansell SM, et al. Autograft immune content and survival in non-Hodgkin's lymphoma: a post hoc analysis. *Leuk Res*. 2019;81:1–9.
51. Lee SE, Lim JY, Kim TW, et al. Different role of circulating myeloid-derived suppressor cells in patients with multiple myeloma undergoing autologous stem cell transplantation. *J Immunother Cancer*. 2019;7:35.
52. Kabir TF, Kunos CA, Villano JL, Chauhan A. Immunotherapy for medulloblastoma: current perspectives. *Immunotargets Ther*. 2020;9:57–77.
53. Voskamp MJ, Li S, van Daalen KR, Crnko S, ten Broeke T, Bovenschen N. Immunotherapy in medulloblastoma: current state of research, challenges, and future perspectives. *Cancers*. 2021;13:5387.
54. Papageorgiou GI, Razis ED. CNS tumors in adolescents and young adults: the need for a holistic specialized approach. *JCO Oncol Pract*. 2020;16:155–162.
55. Merchant TE, Pollack IF, Loeffler JS. Brain tumors across the age spectrum: biology, therapy, and late effects. *Semin Radiat Oncol*. 2010;20:58–66.
56. Stiff PJ, Micallef I, Nademanee AP, et al. Transplanted CD34(+) cell dose is associated with long-term platelet count recovery following autologous peripheral blood stem cell transplant in patients with non-Hodgkin lymphoma or multiple myeloma. *Biol Blood Marrow Transplant*. 2011;17:1146–1153.
57. Jillella AP, Ustun C. What is the optimum number of CD34+ peripheral blood stem cells for an autologous transplant? *Stem Cells Dev*. 2004;13:598–606.
58. Pavone V, Gaudio F, Console G, et al. Poor mobilization is an independent prognostic factor in patients with malignant lymphomas treated by peripheral blood stem cell transplantation. *Bone Marrow Transplant*. 2006;37:719–724.
59. Costa LJ, Nista EJ, Buadi FK, et al. Prediction of poor mobilization of autologous CD34+ cells with growth factor in multiple myeloma patients: implications for risk-stratification. *Biol Blood Marrow Transplant*. 2014;20:222–228.
60. Knight TE, Chiengthong K, Wall DA, et al. Effect of autograft CD34 + dose on outcome in pediatric patients undergoing autologous hematopoietic stem cell transplant for central nervous system tumors. *Transplant Cell Ther*. 2022;28(Suppl):S252–S253.
61. Knight TE, Chiengthong K, Wall DA, et al. Impact of CD34+ cell dose on outcome among children undergoing autologous hematopoietic stem cell transplant for high-risk neuroblastomas. *Transplant Cell Ther*. 2022;28(Suppl):S251–S252.