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Pineoblastoma in Children Less Than Six Years of Age: The Head Start I, II and III Experience

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Abstract

BACKGROUND: We report the outcomes of patients with pineoblastoma and trilateral retinoblastoma syndrome enrolled on the Head Start (HS) I-III trials.

METHODS: Twenty-three children were enrolled prospectively between 1991–2009. Treatment included maximal surgical resection followed by 5 cycles of intensive chemotherapy and consolidation with marrow-ablative chemotherapy and autologous hematopoietic cell rescue (HDCx/AuHCR). Irradiation following consolidation was reserved for children over 6 years of age or those with residual tumor at the end of induction.

RESULTS: Median age was 3.12 years (range: 0.44–5.72). Three patients withdrew from the study treatment and 2 patients experienced chemotherapy-related death. Eight patients experienced progressive disease (PD) during induction chemotherapy and did not proceed to HDCx/AuHCR.

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Conflict of Interest: Ira J. Dunkel is a consultant for Apexigen, Bayer, and Celgene (all unpaid or de minimis compensation). All other authors have no conflicts of interests to disclose.

Ten patients received HDCx/AuHCR; 8 experienced PD post-consolidation. Seven patients received craniospinal irradiation (CSI) with median dose of 20.7 Gy (range, 18–36 Gy) with boost(s) (median dose 27 Gy, range, 18–36 Gy); 3 received CSI as adjuvant therapy (2 post-HDCx/AuHCR) and 4 upon progression/recurrence. The 5-year progression-free survival (PFS) and overall survival (OS) were 9.7% (95%, CI: 2.6–36.0%) and 13% (95%, CI: 4.5–37.5%), respectively. Only 3 patients survived beyond 5 years. Favorable OS prognostic factors were CSI (hazard ratio (HR)=0.30 (0.11–0.86), $p=0.025$), and HDCx/AuHCR (HR=0.40 (0.16–0.99), $p=0.047$).

CONCLUSIONS: Within the HS I-III trials, CSI and HDCx/AuHCR were statistically associated with improved survival. The high PD rate during later induction cycles and following consolidation chemotherapy warrants consideration of fewer induction cycles prior to consolidation and the potential intensification of consolidation with multiple cycles of marrow-ablative chemotherapy and irradiation.

Keywords

Autologous hematopoietic cell rescue; Craniospinal irradiation; Head Start; Marrow-ablative chemotherapy; Pineoblastoma

Introduction

Pineoblastoma is a malignant embryonal tumor of the pineal region that comprises less than 1% of overall primary brain tumors.¹ Pineoblastoma occurs more frequently in children and young adults.² Standard therapy for older children and adolescents includes maximal safe surgical resection followed by craniospinal irradiation (CSI) and chemotherapy.³ Pineoblastoma behaves differently among infants and younger children who suffer worse outcomes, especially when no radiotherapy is administered during initial therapy.^{3,4} Given the well-known and significant side-effects of brain irradiation on young children, the Head Start (HS) protocols have utilized an irradiation-sparing strategy.^{5,6} The HS protocols utilize high-dose induction chemotherapy followed by marrow-ablative chemotherapy and autologous hematopoietic cell rescue (HDCx/AuHCR). Herein, we present the outcomes of patients with pineoblastoma treated prospectively on three sequential multi-institutional HS trials (HS-I, II and III). The data for 21 out of the 23 patients enrolled in HS I-III was discussed in two earlier studies.^{3,7} However, we provide here a more detailed and expanded analysis.

Methods

Informed Consent

Institutional review board (IRB) approval at the treating institution was required before enrolling any child in all the HS I-III trials. Parents/legal guardians signed an informed consent form and assent (as required by local IRB policies) before enrolling any patient.

Eligibility and Staging

Patients younger than 6 years of age with newly-diagnosed pineoblastoma were eligible. The staging of all patients was classified using the Chang tumor M-staging system.⁸ Maximal safe surgical resection was encouraged at diagnosis. All patients underwent brain and whole spine magnetic resonance imaging (MRI) with/without gadolinium, and lumbar cerebrospinal fluid (CSF) analysis on or after postoperative day 14 to evaluate the extent of disease. Surgical resection was defined as a gross total resection (GTR) if there was no visible tumor on postoperative imaging studies; near-total resection (NTR) if tumor resection was more than 95% of the tumor with evidence of residual tumor; subtotal resection (STR) if tumor resection was between 50% and 95%; partial resection if resection was between 10–50% of the tumor; and biopsy if resection was less than 10% of the tumor.

Treatment

All patients were treated according to three sequential non-randomized multi-institutional studies, HS-I (1991–1997), HS-II (1997–2003)* and HS-III (2003–2009) ([Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00392886); [NCT00392886](https://clinicaltrials.gov/ct2/show/study/NCT00392886)). After maximal safe surgical resection, children received 5 cycles of induction chemotherapy followed by a consolidating cycle of HDCx/AuHCR. Second-look surgery was recommended if there was evidence of residual tumor after the completion of induction chemotherapy. Radiotherapy was reserved for children over 6 years of age at diagnosis or those with residual tumor prior to consolidation. Induction chemotherapy regimens varied among the three trials. The induction regimens included regimen A, A2, D, and D2 as discussed in previous publications.^{9–12} On HS-I/HS-II induction chemotherapy regimen A consisted of five cycles of intravenous vincristine, cisplatin, cyclophosphamide, and etoposide. High-dose methotrexate was added for metastatic patients in all induction cycles in HS-II regimen A2. In HS-III regimen D, cycles 1, 3, and 5 were identical to HS-II regimen A2; however, cycles 2 and 4 consisted of oral etoposide and temozolomide in addition to intravenous cyclophosphamide and vincristine, without cisplatin and methotrexate. In HS-III regimen D2, the doses of cyclophosphamide and high-dose methotrexate were modestly reduced. The consolidation chemotherapy was identical in all HS trials which included carboplatin, thiotepa and etoposide followed by a single AuHCR.

Radiotherapy

Patients were eligible to receive radiotherapy based on their age at diagnosis as well as treatment response. Children younger than 6 years of age without evidence of disease at the completion of induction chemotherapy or who achieved complete response (CR) by second-look surgical resection before starting consolidation chemotherapy, did not receive radiotherapy. Otherwise, patients were eligible to receive irradiation after finishing consolidation. The CSI dose ranged between 18–36 Gy with a boost to the primary site of 45–54 Gy.

*HS I and II both trials are not registered in clinicaltrials.gov as both trials were initiated and completed before December 26th 2007.

Response Evaluation

There was no central review of radiographic treatment responses. Two-dimensional response evaluation criteria were undertaken by MRI with and without gadolinium. Response criteria were categorized as follows: CR was defined as a complete disappearance of all previously assessable tumor. Continuous complete response (CCR) was defined as the patient continue to have no evidence of the disease after GTR and chemotherapy. Partial response (PR) was defined as a greater than 50% decrease in the tumor size. Stable disease (SD) was defined as a decrease in the tumor size between 25% and 50% or less than a 25% increase in the tumor size. Progressive disease (PD) was defined as the appearance of any new tumor lesions or greater than 25% increase in tumor size.

Toxicity

The hematopoietic and non-hematopoietic toxicities of the HS I-II chemotherapy regimens were classified on the basis of the Children's Cancer Group Toxicity and Complications Criteria. For patients enrolled in HS-III, the hematopoietic toxicities and non-hematopoietic toxicities of the chemotherapy regimens were classified on the basis of the Common Terminology Criteria for Adverse Events (CTCAE) v3.0.¹³

Follow-Up Imaging

Patients were followed using MRI with and without gadolinium every 3 months during therapy and for the first 2 years following the completion of treatment; then every 4 months through the third year, then every 6 months until 4 years after completion of treatment, and annually thereafter.

Statistical Analysis

Data were summarized using descriptive statistical methods. Intention-to-treat analysis was utilized to minimize bias towards favorable outcomes. The Kaplan-Meier method was used to estimate overall survival (OS) and progression-free survival (PFS) and their corresponding 95% confidence intervals (CI). Patients who did not encounter an event at the time of the last follow-up were considered censored. PFS was defined as the time from the date of diagnosis to progression, relapse, censoring or death from any cause. OS was defined as the time from the date of diagnosis to death or date of last known follow-up. The log-rank test was used to test for differences in survival between patient groups. Cox proportional hazard models were used to assess the impact of demographic, clinical, and treatment-related characteristics on survival by presenting hazard ratios and corresponding 95% CI. Variables found to be significant ($p < 0.05$) on univariate models were considered for a multivariable model. Statistical analyses were performed using the base R statistical package as well as the "survival" and "survminer" R packages (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

Data on 23 children with histologically-confirmed pineoblastoma were available from the three HS trials. The median age at diagnosis was 3.12 years (range 0.44–5.72 years). All patients were younger than 6 years of age; 74% and 48% of the patients were below 4 and 3 years of age, respectively. Twelve patients had localized disease, while 11 had metastatic disease at the time of presentation. Two patients with pineoblastoma had trilateral retinoblastoma syndrome; unilateral or bilateral hereditary retinoblastoma associated with an intracranial primitive neuroectodermal tumor in the pineal region consistent pathologically with pineoblastoma.^{14,15} Histologic central review was only available for three patients. Nine patients received regimen A, 4 patients received regimen A2, 5 patients received regimen D, and 5 patients received regimen D2. Patient clinical characteristics are listed in Table 1.

Treatment Response and Outcome

Eight patients received five cycles of induction chemotherapy then proceeded to HDCx/AuHCR. Two patients enrolled in HS-I trial proceeded to HDCx/AuHCR directly after 3 and 4 cycles of induction chemotherapy which was major deviation protocol-defined treatment. Five patients did not complete the treatment protocol for multiple reasons; death secondary to chemotherapy-related toxicity (n=2), early withdrawal during cycle 1 due to PD (n=1), and late withdrawals post-cycle 5 after achieving CR/CCR and before starting HDCx/AuHCR secondary to chemotherapy-related toxicities (n=2). Eight patients did not proceed to HDCx/AuHCR secondary to PD during or after induction chemotherapy; 6 patients had PD post-cycle 5, 1 post-cycle 4, and 1 post-cycle 1.

Nineteen patients relapsed in the following sites: local site only (n=4), distal site only (n=6), combined local and distal sites (n=9). Fig. 1 provides a summarized flow diagram of the 23 patients with pineoblastoma enrolled in the HS I-III protocols. Supporting Information Table S1 provides detailed information on the individual patient demographics, diagnostic and treatment characteristics.

Three patients were long-term survivors with a median follow-up of 157.9 months (range, 66.25–159 months). Two of the long-term survivors received regimen A and the third survivor was enrolled on regimen A2. One patient received HDCx/AuHCR but no irradiation and was alive at 159 months during the latest follow-up. The second survivor had metastatic disease at presentation, received both HDCx/AuHCR and CSI, and was alive without disease at 157.9 months at the latest follow-up. The third survivor was reported to have experienced PD in the spine after cycle 1 of regimen A2, and then received brain irradiation (36 Gy), tumor bed boost (18 Gy), spinal irradiation (45 Gy) with lower-end spinal boost (5.4 Gy). This patient continued to be alive at 66.3 months at latest the follow-up.

The 3- and 5-year PFS for the 23 patients were 14.5% (95%CI: 5.1–41.2%) and 9.7% (95%CI: 2.6–36.0%), respectively (Fig. 2). The 3- and 5-year OS were 17.4% (95%CI: 7.1–42.4%) and 13% (95%CI: 4.5–37.5%), respectively (Fig. 2). The median time to progression

for the 19 patients with PD was 7.5 months (range: 0.36–52.4 months). The specific median PFS and OS for each HS regimen are detailed in Supporting Information Table S2.

There were no statistical differences in 3- and 5-year PFS and OS among the 23 patients by the age of presentation or metastatic staging. Univariate and multivariable Cox analyses demonstrated that use of CSI and HDCx/AuHCR were the only prognostic factors associated with a positive impact on OS (Table 2), and only HDCx/AuHCR was associated with a positive impact on PFS *via* univariate analysis (Table 3).

Patients with localized disease and less than GTR (n=7) had a better 3- and 5- year PFS and OS compared to patients who had a GTR (n=5) (Supporting Information Figure S1, S2). This observation is counterintuitive and may be a result of the small sample size of patients with localized disease as the CI was wide. Therefore, this observation is not clinically significant. The univariate Cox analysis did not show any significant statistical difference in the PFS or OS amongst all patients with localized or metastatic disease when stratified by the extent of surgical resection (Tables 2, 3).

Seven patients received CSI with a median dose of 20.7 Gy (range: 18–36 Gy), with boost(s) (median dose=27 Gy; range: 18–36 Gy). Four patients received CSI upon progression/recurrence. Three patients received irradiation as adjuvant therapy, 2 of whom received CSI post-HDCx/AuHCR; the irradiation dosage was not available for 1 patient. Patients who received CSI had 3- and 5-year OS of 42.9% (95% CI: 18.2–100%) 28.6% (95% CI: 8.9–92.2%), respectively, compared with 3- and 5-year OS of 6.3% (95% CI: 0.9–41.7%) for both among patients who did not receive any irradiation (p= 0.019) (Fig. 3). Nevertheless, no statistical difference in the 3- and 5-year PFS was observed between the two groups (Fig. 3).

Ten patients received 1 cycle of HDCx/AuHCR. Eight of the 10 patients developed PD post-AuHCR. Six of the 12 patients with localized disease at diagnosis proceeded to HDCx/AuHCR; five of these 6 patients achieved initially CR/CCR post-transplant. The median progression time post-AuHCR was 12 months (range: 5–25 months). The 3- and 5-year PFS of patients who received 1 cycle of HDCx/AuHCR was 20.0% (95% CI: 5.8–69.1%) for both compared with 3-year PFS of 9.7% (95% CI: 1.5–61.8%) and 5-year PFS of 0% among patients who did not receive HDCx/AuHCR (p= 0.0025) (Fig. 3). Moreover, patients who received 1 cycle of HDCx/AuHCR had 3- and 5-year OS of 20.0% (95% CI: 5.8–69.1%) for both compared with 3-year OS of 15.4% (95% CI: 4.3–55.0%) and 5-year OS of 7.7% (95% CI: 1.2–50.6%) among patients who did not receive HDCx/AuHCR (p= 0.041) (Fig. 3).

Toxicities

The toxicities of HS regimens have been reported in earlier publications.^{10–12} Adverse events were not available for 3 patients. Two patients, both enrolled on the HS III protocol, died from therapy-related toxicity. One patient received 3 cycles of regimen D and expired secondary to sepsis. The second patient died due to multiple organ dysfunction secondary to toxic epidermal necrosis during cycle 2 of regimen D2. Grade 3/4 hematopoietic toxicities were reported in 100% of the patients. All chemotherapy-related acute toxicities resolved except for the two patients mentioned earlier who experienced toxic deaths (see Supporting

Information Table S3 for more details). Acute toxicities related to radiotherapy were limited to irradiation-associated encephalopathy in 1 patient.

Discussion

The outcomes of young children with pineoblastoma enrolled in the HS I-III trials were unsatisfactory and similar to the outcomes reported in other trials.^{3,7,16–20} Age at presentation was a major risk factor with the strongest impact on the outcome, independent of the treatment modality.³ Multiple studies demonstrated that younger patients (typically less than 4 or 5 years old) had worse outcomes compared with older children.^{4, 21} There was no statistical difference in outcomes among our patients when they were stratified by their age at presentation. All patients were less than 6 years of age, therefore, already representing a higher-risk group.

Radiotherapy is a major component of pineoblastoma standard treatment. Patients with pineoblastoma experience an increased risk of distant dissemination; therefore, CSI has been recommended to prevent distant relapse.^{17, 22} CSI in infants and young children, even when utilizing a risk-adapted approach, is associated with neurocognitive decline and neurodevelopmental deficits that are known to significantly impair the child's quality of life.^{16, 23} Accordingly, CSI is usually avoided or delayed to reduce the risk of neurotoxicity among young children whenever possible. In our cohort, only 3 patients received CSI before tumor progression, which limited our ability to draw any conclusions in regards to radiotherapy. However, CSI was associated with statistically significant improved OS, but not PFS.

The role of focal radiotherapy was analyzed in the SJYC07 multi-center trial; 12 patients with pineoblastoma (3 years of age or younger) received chemotherapy; 6 of the 12 patients received focal radiotherapy.²⁴ Eleven out of the 12 patients experienced PD.²⁴ In the Children's Oncology Group (COG) ACNS0332 trial, 8 out of 29 patients with pineoblastoma were between 3–6 years of age with a median age of 3.45 years (range: 3–5.9 years).²⁵ These 8 patients received upfront surgical resection followed by CSI of 36 Gy with a tumor bed boost to 55.8 Gy combined with vincristine with or without carboplatin radiosensitization. They subsequently received 6 cycles of maintenance chemotherapy with or without adjuvant isotretinoin.²⁵ All patients were alive at the time of publication with a median OS of 72.3 months (range: 24.8–106.6 months).²⁵ This strongly suggests the benefit of CSI in improving survival outcomes in children 3 years of age or older with pineoblastoma. However, the results of the ACNS 0332 trial cannot be compared with either the HS I-III trials or the SJYC07 trial, as the population was older and did not include any patients below 3 years of age.

In earlier retrospective and prospective reports, HDCx/AuHCR was associated with favorable outcomes among patients with pineoblastoma.^{26, 27} In a recent pooled analysis, the effect of HDCx/AuHCR on the outcomes was more pronounced in the older age group or patients with metastases.³ Among our patients, HDCx/AuHCR was associated with a positive impact on both PFS and OS. However, this association may not imply causation, as 8 patients (35%) did not proceed to HDCx due to early PD. This might be attributed

to different tumor biology among patients who proceeded to HDCx, and therefore might have less aggressive tumors compared to patients who did not proceed to HDCx. In the pooled analysis, it was observed that a small group of young patients with localized disease survived after receiving both HDCx/AuHCR and focal irradiation.³ This combination is worth investigating, given that it may provide a less neurotoxic treatment modality while providing good outcomes.

The high progression rate post-HDCx/AuHCR (80%) in our cohort indicates that one cycle of consolidation was not sufficient to provide any long-term survival. Hence, other consolidation modalities post-HDCx/AuHCR should be investigated, such as post-consolidation irradiation, post-consolidation maintenance chemotherapy, or intensification of consolidation with multiple cycles of HDCx.

Pineoblastoma in infants and young children are more aggressive and less responsive to chemotherapy compared with adolescents and adults.^{3,18,19} In our trials, the median time to progression was 7.5 months (range: 0.36–52.4 months). Eight patients experienced PD during induction chemotherapy. This observation is in line with the results of earlier trials.^{18,19} Incorporating shorter dose-intensive induction chemotherapy that is administered in 2 to 3 cycles of 21–28 days may increase the proportion of patients who proceed to HDCx/AuHCR. Another option would be earlier administration of CSI followed by induction chemotherapy and HDCx/AuHCR among children aged 3 years of age or older.

In our cohort, the extent of the tumor surgical resection did not improve the outcomes of patients with localized disease, consistent with previous trials.^{3,16,22,28} However, other reports showed the significance of the extent of resection on the outcomes. A single-center retrospective analysis reported improved outcomes among patients above 5 years of age with localized disease who achieved GTR of their primary tumor.²⁹ The COG 99701 trial found that GTR was a positive prognostic factor among older patients with local disease.³⁰ The recent ACNS0332 trial showed that patients with supratentorial primitive neuroectodermal tumor (CNS- PNET) and pineoblastoma with residual disease greater than 1.5 cm² had better OS compared with patients with residual disease less than 1.5 cm².²⁵ Therefore, we recommend pursuing an upfront maximal surgical resection and a second-look surgical resection early into the induction chemotherapy phase whenever deemed safe and feasible.

Incorporating biological and molecular studies in the design of future trials will be essential to better understand the nature of this tumor and the unique characteristics of the survivors. DNA methylation profiling in the SJYC07 trial for children less than 3 years of age showed marked molecular heterogeneity and clustering of pineoblastoma with high-risk medulloblastoma groups and choroid plexus tumors.²⁴ In the ACNS0332 trial, DNA methylation profiling of 29 pineoblastoma patients, 3 years of age or older, demonstrated that 26 had pineoblastoma while the remaining three patients had medulloblastoma (n=1) and atypical teratoid rhabdoid tumor (n=2).²⁵ These results may indicate that pineoblastoma in children less than 3 years of age may differ biologically compared to those older than 3 years of age, which may accordingly explain their worse outcomes.

The HS trials included 2 patients with pineoblastoma presenting as trilateral retinoblastoma syndrome; 1 patient with M0 disease expired after cycle 3 of chemotherapy secondary to septic shock, and 1 patient with M3 disease experienced PD after cycle 5 before receiving HDCx/AuHCR. Accordingly, no conclusions can be drawn from these 2 patients.

Our study has multiple limitations that must be acknowledged. Selection bias may be introduced due to the limited number of institutions that participated in the HS I-III protocols. The low accrual rate may have also played a role given that only 23 patients were enrolled over 18 years secondary to the rarity of the disease. Moreover, neither central pathological nor neuroradiological review were available for the majority of the patients. Molecular analysis and diagnostic reevaluations of the tumor specimens were not possible as tumor material retrieval was not feasible.

In conclusion, the outcomes of children less than six years of age with pineoblastoma enrolled in the HS I-III trials were unsatisfactory and similar to the outcomes of earlier trials. CSI and/or HDCx/AuHCR were the only factors associated with improved outcomes in our patients. However, the positive impact on outcomes observed with HDCx/AuHCR may not indicate causation as the HS I-III trials had multiple limitations as mentioned earlier. From the available literature, CSI improved the survival outcomes in children 3 years of age or older with pineoblastoma. Among children less than 3 years of age, administering CSI is limited by the expected long-term side effects. Therefore, treatment modalities including HDCx/AuHCR may provide a tool to delay the administration of CSI or focal irradiation. Future trials need to explore shorter and more intensive chemotherapy regimens to address the early chemotherapy failure rates noticed among young patients. Moreover, the high rate of progression post-consolidation HDCx/AuHCR may indicate the need to investigate post-consolidation maintenance therapies or intensification of consolidation with multiple cycles of HDCx/AuHCR. Finally, including molecular profiling in all prospective clinical trials is necessary to better understand the tumor biology and to help develop more effective treatment modalities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AuHCR	Autologous hematopoietic cell rescue
CI	Confidence intervals
CNS	Central Nervous System
CNS- PNET	Central nervous system supratentorial primitive neuroectodermal tumor
COG	Children's Oncology Group
CR	Complete response
CSF	Cerebrospinal fluid
CSI	Craniospinal irradiation
CTCAE	Common Terminology Criteria for Adverse Events
GTR	Gross total resection
HDCx	Marrow-ablative chemotherapy
HS	Head Start
IRB	Institutional review board
MRI	Magnetic resonance imaging
NTR	Near-total resection
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
STR	Subtotal resection

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AuHCR: Autologous hematopoietic cell rescue; CCR: continuous complete response; CR: complete response; CSI: craniospinal irradiation; GTR: gross total resection; <GTR: less than gross total resection; HDCx: Marrow-ablative chemotherapy; MODS: multiple organ dysfunction syndrome; N/A: not available; ND: not done; PD: progressive disease; PR: partial response; SD: stable disease; TD: toxic death; TEN: toxic epidermal necrolysis

^a Surgical outcome is the final surgical outcome of the primary tumor outcome which may be achieved after upfront or delayed surgical resection. Post-induction and post-transplant are overall response of the patients.

^b One patient received regimen A for cycle 1,2 then received regimen A2 for 3,4 and methotrexate was held on cycle 5.

^c Patient received CSI upon disease progression

^d The alive patient received 4 cycles of regimen A, HDCx/AuHCR and no CSI.

^e Patient received CSI as adjuvant therapy.

^f Patient received CSI after disease relapse.

^g The alive patient received 1 cycle of regimen A2 then received CSI and no HDCx/AuHCR.

^h Patient had trilateral retinoblastoma.

ⁱ One of the three patients had trilateral retinoblastoma.

^j Parents withdrew this patient who did not undergo upfront surgical resection from the study on day 5 of cycle 1 due to PD.

Figure 1.

Flow diagram of the 23 patients with pineoblastoma enrolled in the HS I-III trials.

Figure 2. Progression-free survival and overall survival for the 23 patients with pineoblastoma enrolled in the Head Start I-III trials.

Figure 3.

Progression-free and overall survival of the 23 patients with pineoblastoma enrolled in the Head Start I-III (A,B) stratified by craniospinal irradiation and (C,D) stratified by marrow-ablative chemotherapy followed by autologous hematopoietic cell rescue.

TABLE 1

Characteristics of the HS I-III studied populations

	Head Start I	Head Start II	Head Start III	Total
Regimen				
A	4	5 ¹	-	9
A2	-	4	-	4
D	-	-	5	5
D2	-	-	5 ²	5
Age at diagnosis				
Median (Years)	2.8	2.2	3.6	3.1
Mean (Years)	3.1	2.5	3.4	3.0
< 4 years	3	8	6	17
> 4 years	1	1	4	6
Sex				
Female	2	5	4	11
Male	2	4	6	12
Primary tumor location				
Pineal gland only	4	9	8	21
Trilateral retinoblastoma syndrome	-	-	2	2
Metastasis disease at diagnosis				
M0	3	5	4	12
M1	-	1	2	3
M2	-	1	-	1
M3	1	2	4	7
M4	-	-	-	-
Cerebrospinal fluid cytology				
Positive	1	4	6	11
Negative	3	5	4	12
Extent of surgical resection				
Gross total resection	1	5	2	8
Subtotal resection	3	4	8	15
Radiotherapy				
Yes	1	4	2	7
No	3	5	8	16

¹ One patient in the Head Start II protocol received initially two cycles of regimen A then received two cycles of regimen A2 and in the last cycle methotrexate was held.

² One patient withdrew after day five of cycle one of D2 regimen.

TABLE 2

Cox Proportional hazard models of overall survival for multiple prognostic factors among the 23 patients with pineoblastoma enrolled in HS I-III.

Cox Proportional Hazard Models for Overall Survival				
	Univariate Analysis		Multivariable Analysis	
Characteristic	HR (95% CI)	p-value	HR (95% CI)	p-value
Age >4 at diagnosis	0.35 (0.11 – 1.13)	0.08	-	-
Metastatic disease vs. localized disease	0.72 (0.29 – 1.79)	0.48	-	-
Radiotherapy	0.30 (0.11 – 0.86)	0.0254	0.06 (0.01 – 0.34)	0.0014
HDCx + AuHCR	0.40 (0.16 – 0.99)	0.0477	0.08 (0.02 – 0.39)	0.0019
Less than GTR <i>versus</i> GTR	0.61 (0.24 – 1.54)	0.29	-	-

AuHCR: Autologous hematopoietic cell rescue; CI: Confidence Interval; HDCx: myeloablative chemotherapy; HR: Hazard Ratio; GTR: Gross Total Resection.

TABLE 3

Cox Proportional hazard models of progression-free survival for multiple prognostic factors among the 23 patients with pineoblastoma enrolled in HS I-III.

Cox Proportional Hazard Models for Progress-Free Survival				
	Univariate Analysis		Multivariable Analysis	
Characteristic	HR (95% CI)	p-value	HR (95% CI)	p-value
Age >4 at diagnosis	0.50 (0.16 – 1.57)	0.24	-	-
Metastatic disease vs. localized disease	0.81 (0.33 – 2.02)	0.66	-	-
Radiotherapy	0.40 (0.14 – 1.15)	0.09	-	-
HDCx + AuHCR	0.23 (0.09 – 0.59)	0.0024	-	-
Less than gross total resection vs. gross total resection	0.78 (0.31 – 1.95)	0.60	-	-

AuHCR: Autologous hematopoietic cell rescue; CI: Confidence Interval; HDCx: myeloablative chemotherapy; HR: Hazard Ratio.