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RESEARCH ARTICLE

Group 4 Medulloblastomas of Early Childhood Treated With High-Dose Chemotherapy- and Craniospinal Irradiation-Sparing Approach

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Abbreviations: CI, confidence interval; CSI, craniospinal irradiation; fRT, focal radiotherapy; FSIQ, full-scale intellectual quotient; GTR, gross total resection; HDC, high-dose chemotherapy; HD MTX, high-dose methotrexate; HR, high risk; HS, head start; iMB, infant medulloblastoma; IT/IV, intrathecal/intraventricular; MB, medulloblastoma; OS, overall survival; PFS, progression-free survival; PRS, post-relapse survival; SIOP, International Society of Pediatric Oncology; SR, standard risk; TEC, thiotepa, etoposide, carboplatin; TLDA, TaqMan Low-Density Array; VIF, variance inflation factors.

ABSTRACT

Background: Group 4 medulloblastoma (MB) is rare in young children. Data on craniospinal irradiation (CSI)-sparing approaches are limited.

Methods: This multicenter study reported outcomes for patients younger than 7 years old with Group 4 MB treated with high-dose chemotherapy (HDC) without adjuvant CSI.

Results: Thirty-eight patients were included (26 M/12 F). Median age at diagnosis was 46.4 months (25.9–78), with 24% ≤36 months. Twenty-four patients (63.2%) had localized disease. Fourteen (36.8%) presented with metastatic disease, and 26 (68.4%) underwent gross total resection (GTR). The most used HDC regimens were carboplatin/thiotepa (76.3%) and carboplatin/thiotepa/etoposide (21.1%). Twenty (52.6%) relapses occurred at a median 21.9 months (5–99.8) from diagnosis. Patients with upfront GTR and/or who received three cycles of HDC had better PFS ($p = 0.02$ and $p = 0.002$, respectively). Local relapse accounted for 45%. Eighteen patients received salvage therapy with curative intent, all with radiotherapy (16 = CSI, 2 = focal). The CSI dose ranged from 18 to 36 Gy, and 43.7% received ≤23.4 Gy. Patients who underwent salvage surgery and/or chemotherapy were more likely to receive CSI ≤23.4 Gy ($p = 0.008$ and $p = 0.03$). The 5-year post-relapse survival and overall survival (OS) were, respectively, 60.3% (95% confidence interval [CI]: 26.9–82) and 72.7% (95% CI: 51.9–85.7). The 5-year CSI-free OS was 69.7% (95% CI: 39.1–87.1).

Conclusion: High dose chemotherapy for Group 4 MB was associated with a relapse rate of 52.6%, which favorably compares to data reported with conventional chemotherapy. Salvage radiotherapy retrieved more than two-thirds of the patients. Half of the survivors never received radiotherapy. Such an approach may represent an alternative to upfront CSI for young children with Group 4 MB.

1 | Introduction

About one-third of medulloblastomas (MB) occur in patients under 3 years of age and 50% under 5 years of age [1–3]. Among the MB of early childhood or infant MB (iMB), the sonic hedgehog (SHH) and Group 3 molecular subgroup account for 45%–50% and 25%–30%, respectively. In contrast, Group 4 MB is less frequent. Hicks et al. reported a frequency of 13.7% in a large cohort of 202 young children diagnosed with molecularly characterized MB before the age of 5 years [4], while frequencies described on recent prospective iMB trials ranged from 5.2% to 12.5% [5–7]. Prior to the now more routine molecular characterization, all iMB patients were treated with "infant strategies" aiming at deferring or avoiding the use of craniospinal irradiation (CSI), irrespective of molecular subgrouping. Outcomes of SHH or Group 3 iMB treated with these infant strategies, such as high-dose chemotherapy and stem cell transplantation (HDC) or conventional chemotherapy with serial intrathecal injections of chemotherapy, have been reported [5–9]. However, due to the small number of young children with Group 4 MB, very little data are available to assess the impact of CSI-sparing approaches in this population. In this report, we describe the outcome of young patients with Group 4 MB treated with HDC strategies without adjuvant CSI and investigate possible prognostic factors associated with survival.

2 | Materials and Methods

2.1 | Study Participants

We retrospectively assembled an international multicenter cohort including patients younger than 7 years of age, diagnosed between 2001 and 2023 with a molecularly characterized Group 4 MB, and treated with HDC for a CSI-sparing approach. Patients treated with adjuvant focal radiotherapy (fRT) were eligible. Following ethics approval at each participating center, patients' demographics, institutional pathology and molecular report, initial treatment, management at relapse, and outcomes post upfront adjuvant treatment and post-relapse were collected (Table S1). Deidentified neurocognitive evaluations and audiograms were also collected when available. Audiograms were graded with the Boston SIOP (International Society of Pediatric Oncology) ototoxicity scale using the best ear [10].

2.2 | Statistical Analysis

Descriptive statistics were reported using median and range for continuous variables and frequencies and percentages for categorical variables. Chi-square and Fisher's exact tests were used to compare categorical variables between groups. Overall survival (OS), progression-free survival (PFS), and post-relapse survival (PRS) were analyzed using Kaplan–Meier plots and log-rank tests to compare survival between groups. OS was calculated from the date of diagnosis to the date of last follow-up or date of death from any cause. PFS was calculated from the date of initial diagnosis to the date of earliest radiologic disease progression or relapse. PRS was defined as the time from first relapse to death or last follow-up and was assessed for patients who received salvage therapy with curative intent. CSI-free overall survival was calculated from the date of diagnosis to the last follow-up or death for all patients irrespective of relapse status, with death as the event. Kaplan–Meier survival estimates were generated for patients who did not receive CSI (CSI-free survival) versus those who received CSI. Patients who only received focal RT at initial treatment or at relapse were included in the non-CSI group. Univariate and multivariate Cox proportional hazards regression were performed. Variables not significant in the univariate analysis were excluded from the multivariate analysis. Potential confounders, including age, sex, risk stratification, and presence of metastasis at diagnosis, were

selected based on clinical relevance and included in the analysis. Collinearity was evaluated using variance inflation factors (VIF) with a cutoff point set at less than 5. Collinear variables were excluded from the multivariable analysis. A *p*-value less than 0.05 was considered statistically significant. STATA 18.0 was used for all statistical analyses.

3 | Results

3.1 | Patient Characteristics and Initial Treatment

The study included 38 patients from 19 international institutions. The median age at diagnosis was 46.4 months (range: 25.9–78), and 23.7% were ≤3 years old. Patients' characteristics are presented in Table 1. Institutional molecular characterization was obtained through various platforms, including methylation array (60%), Nanostring (26%), TaqMan Low Density Array (TLDA) (11%), and Oncoplex in (3%). Gross total resection (GTR) of the primary tumor was achieved in 26 patients (68.4%). Twenty patients (52.6%) had high-risk disease (metastatic and/or <GTR), while 18 (47.4%) were standard risk (localized and GTR).

Eleven patients (28.9%) received treatment based on the CCG 99703 regimen comprising three induction cycles without high-dose methotrexate (HD MTX), followed by three cycles of high-dose carboplatin and thiotepa and stem cell rescue [11]. Eighteen patients (47.4%) were treated according to the Arm B of ACNS0334 protocol, including three cycles of induction chemotherapy with HD MTX and three cycles of high-dose carboplatin and thiotepa and stem cell rescue [7]. Among these 18 patients, one received only two cycles of consolidation due to renal toxicity. Eight patients (21.1%) were treated according to the Head Start (HS) protocols using HD MTX during induction cycles, followed by a single course of HDC with carboplatin, thiotepa, and etoposide (TEC) and stem cell rescue [8, 9]. One European patient underwent induction chemotherapy with HD MTX followed by one course of HD carboplatin/etoposide and a second course of HD thiotepa/cyclophosphamide. Overall, 27 (71%) patients received HD MTX during induction. Twenty-four (63.2%) underwent three cycles of HDC, six (15.8%) received two cycles, and eight received one cycle (21.1%) of TEC (Figure 1). The group that received only two cycles of consolidation included three patients treated as per ACNS0334, two as per CCG 99703 protocol, and one treated with the European protocol.

Seven patients (18.9%) received intrathecal or intraventricular (IT/IV) chemotherapy with either cytarabine, methotrexate, or topotecan. Following HDC, five patients (13.5%) underwent maintenance therapy, primarily using metronomic regimens such as the modified MEMMAT protocol with or without IT chemotherapy [12]. Two patients underwent adjuvant focal radiotherapy (fRT). At the end of initial therapy, 34 patients (89.5%) achieved complete remission, two had less than a complete response, one experienced disease progression, and response status was unknown for one patient.

TABLE 1 | Patient characteristics and initial treatment.

Patient characteristics	*N* = 38 (%)
Sex	
Male	26 (68.4%)
Female	12 (31.6%)
Median age at diagnosis	46.4 (25.9–78 months)
≤36 months	9 (23.7%)
>36 months	29 (76.3%)
Surgical resection	
GTR	26 (68.4%)
<GTR	12 (31.6%)
Metastatic status	
M0	24 (63.2%)
M1	1 (2.6%)
M2	2 (5.3%)
M3	11 (28.9%)
Risk stratification	
SR	18 (47.4%)
HR	20 (52.6%)
Histology	
Classical NOS	34 (89.5%)
LCA	3 (7.9%)
ND/MBEN	1 (2.6%)
HD MTX during induction	
Yes	27 (71.1%)
No	11 (28.9%)
HDC regimen	
Carboplatin/Thiotepa	29 (76.3%)
Carboplatin/Thiotepa/Etoposide	8 (21.1%)
Other[a]	1 (2.6%)
Number of cycles of HDC	
3 cycles	24 (63.2%)
<3 cycles	14 (36.8%)
Protocols used	
As per ACNS 0334	18 (47.4%)
As per CCG 99703	11 (28.9%)
As per Head Start	8 (21.1%)
Other	1 (2.6%)
IT chemotherapy	
Yes	7 (18.4%)
No	30 (78.9%)
NA	1 (2.6%)
Maintenance chemotherapy	
No	29 (84.2%)
Yes	5 (13.2%)

(Continues)

TABLE 1 | (Continued)

Patient characteristics	*N* = 38 (%)
Adjuvant focal RT	
Yes	2 (5.3%)
No	35 (92.1%)
NA	1 (2.6%)

Abbreviations: BVZ, bevacizumab; CPM, cyclophosphamide; GTR, gross total resection; HDC, high-dose chemotherapy; HD MTX, high-dose methotrexate; HR, high risk; IT, intrathecal; LCA, large cell anaplastic; M0, no metastasis; M+, with metastasis; MEMMAT, Medulloblastoma European Multitarget Metronomic Anti-Angiogenic Trial; NA, not available; ND/MBEN, nodular desmoplastic/medulloblastoma with extensive nodularity; NOS, not otherwise specified; RT, radiation therapy; SR, standard risk; TMZ, temozolamide; VP16, etoposide.

[a]One cycle of HD carboplatin/etoposide and one cycle with HD thiotepa/cyclophosphamide.

3.2 | Pattern of Relapse and Salvage Therapy

Twenty patients (52.6%) relapsed at a median time of 21.9 months from diagnosis (range: 5–99.8) and 14 months from completion of initial therapy (range: 0–82.8 months). Two patients relapsed 5 years or more after diagnosis. The median age at relapse was 5.9 years (range: 3–13 years). Relapses were local, distant, or combined in 45%, 35%, and 20%, respectively. Thirteen of the 24 patients (54.2%) with initial localized disease relapsed, including nine local (69.2%), three distant (23.1%), and one combined relapse (Figure 2A). Half of the 14 patients with initial metastatic disease relapsed, all with distant recurrence.

Upon relapse, two patients underwent palliative therapy and subsequently died of the disease. Both were metastatic at diagnosis and presented with distant and combined relapses. Eighteen patients underwent salvage therapy with curative intent (Table 2).

TABLE 2 | Modalities of salvage therapies.

Treatment modalities	*N* = 18
Surgery	
Yes	10 (55.6%)
No	8 (44.4%)
Radiation therapy	18 (100%)
Focal	2 (11.1%)
CSI	16 (88.9%)
≤23.4 Gy	7 (38.9%)
36 Gy	9 (50%)
Chemotherapy	
Yes	9 (50%)
No	9 (50%)
Intrathecal chemotherapy	
Yes	1 (5.6%)
No	17 (94.4%)
Maintenance chemotherapy	
Yes	7 (38.9%)
No	11 (61.1%)

Abbreviations: CSI, craniospinal irradiation; Gy, Gray.

Among them, 10 (55.6%) had repeat surgical resection. All underwent salvage radiotherapy (16 CSI and two focal RT). The median age at relapse of patients who received salvage CSI was 6.8 years. In addition to radiotherapy, nine patients (50%) received salvage chemotherapy. Salvage CSI ± boost was administered at a median dose of 36 Gy (range: 18–36 Gy). Thirteen patients (72.2%) received additional tumor boost, given a median dose of 54 Gy (range: 54–58 Gy). Seven patients (43.7%) received a CSI dose ≤23.4 Gy (Figure 2B). In the standard-risk (SR) group, five patients received 36 Gy, one 23.4 Gy, and one 18 Gy CSI. In the high-risk (HR) group,

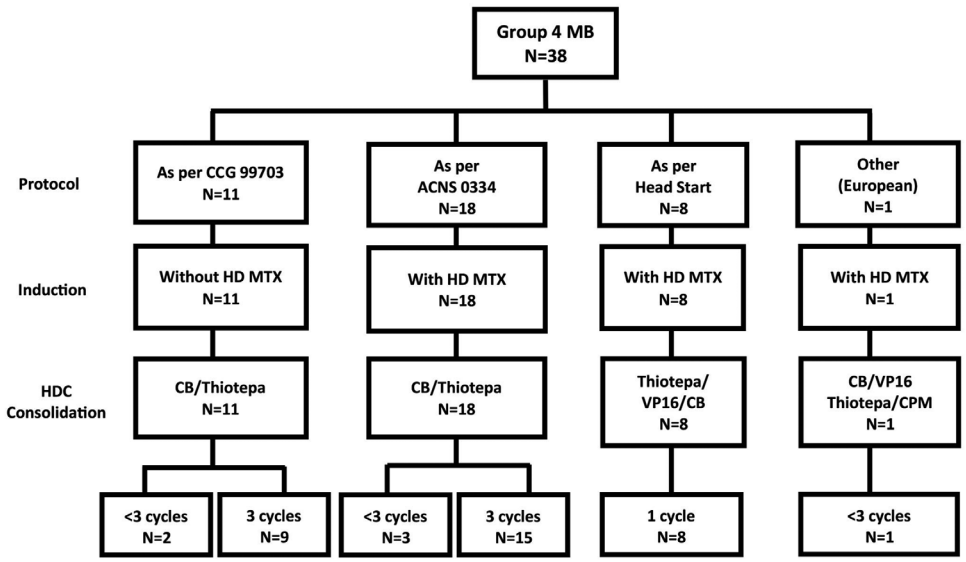

FIGURE 1 | Initial treatment diagram. CB, carboplatin; CPM, cyclophosphamide; HDC, high-dose chemotherapy; HD MTX, high-dose methotrexate; MB, medulloblastoma; VP16, etoposide.

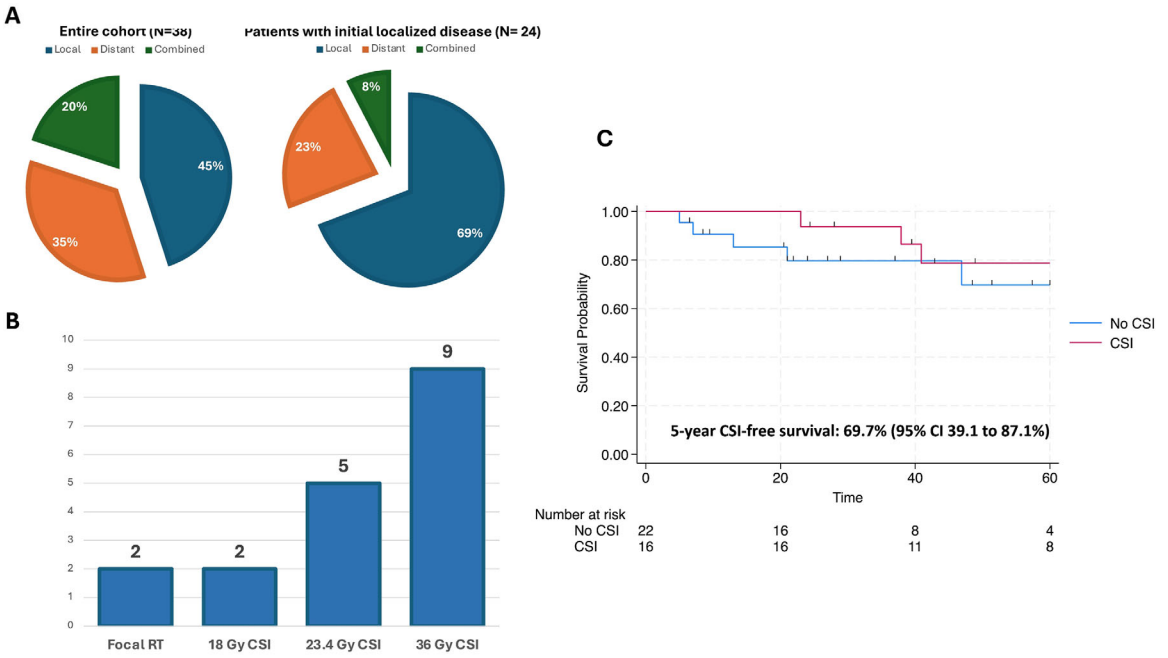

FIGURE 2 | Pattern of relapse (A); doses of salvage RT (B); Kaplan–Meier plot of overall survival according to craniospinal irradiation (CSI) use (C).

four patients received 36 Gy, four 23.4 Gy, and one 18 Gy CSI. Patients who underwent salvage chemotherapy and/or repeated surgery were more likely to receive a CSI dose ≤23.4 Gy ($p = 0.03$ and $p = 0.008$, respectively). No association was found between the dose of salvage CSI and the age at diagnosis ($p = 0.71$), the age at relapse ($p = 0.34$), or the pattern of relapse ($p = 0.17$).

3.3 | Outcome and Prognostic Factors

The 5-year PFS was 41.3% (95% confidence interval [CI]: 23.5%–58.3%) (Figure 3A). Univariate analysis identified upfront GTR ($p = 0.003$), HDC with carboplatin/thiotepa ($p = 0.002$), and consolidation with three cycles of HDC ($p = 0.002$) as factors associated with improved PFS (Table 3). Seven of the eight (87.5%) patients treated as per HS protocols relapsed. HD MTX during induction was not significantly associated with PFS (5-year PFS of 36% with HD MTX vs. 51.9% without HD MTX; $p = 0.20$; Figure 3D, Table 3). The 19 patients (50%) who underwent both GTR and three cycles of HDC had a 5-year PFS of 55.9% (95% CI: 25.9%–77.8%) and a 5-year OS of 85.3% (95% CI: 50.5%–96.4%).

In the multivariate analysis, patients who achieved less than GTR at initial diagnosis had a hazard ratio for relapse of 1.9 (95% CI: 0.71–5.2) compared to those who underwent GTR. Patients who received less than three cycles of HDC showed a hazard ratio for relapse of 3.2 (95% CI: 1.2–8.5) compared to those who received three cycles. HDC regimen and treatment protocols used were collinear with the number of HDC cycles and therefore excluded. Potential confounders, including sex, age, metastatic status at presentation, and risk stratification, were evaluated in multivariate analysis, but did not significantly alter hazard ratio estimates of the significant covariates (Table 3).

The 5-year PRS for the 18 patients who received curative-intent salvage therapy was 60.3% (95% CI: 26.9%–82.3%), with a median follow-up time of 27 months from relapse (range: 2–195.6 months) (Figure S1A).

Twenty-nine patients (76.3%) were alive at the median follow-up time of 40 months (range: 5–217.5) from initial diagnosis. The 5-year OS for the entire cohort was 72.7% (95% CI: 51.9%–85.7%) (Figure S1B). Higher OS was observed for patients who had achieved initial GTR (5-year OS 83.2%, 95% CI: 55.5%–94.4% vs. <GTR 53.5%, 95% CI: 21.2%–77.7%) and for those with SR disease (5-year OS 83.33%, 95% CI: 48.2%–95.6% vs. 64.6%, 95% CI: 36.5%–82.8% for HR disease). Kaplan–Meier survival estimates of prognostic factors for PRS and OS are presented descriptively in Tables S2 and S3.

Nine patients died (23.7%), seven from disease progression, and two from treatment-related toxicity (one from intracranial hemorrhage at the end of consolidation, and one from sepsis during the second cycle of consolidation with carboplatin and thiotepa).

Overall, 22 patients (57.8%), including 11 standard risk (61.1%) and 11 high risk (55%), never received CSI, providing a 5-year CSI-free OS of 69.7% (95% CI: 39.1%–87.1%; Figure 2C). Seventeen of the 29 survivors (58.6%) never received CSI.

3.4 | Neurocognitive Outcome and Ototoxicity Profiles

Nineteen patients (50%) had audiology evaluations. Sixteen of them (84.2%) were assessed by pure tone audiometry, while the remainder were tested with auditory brainstem response, otoacoustic emissions, or behavioral audiometry.

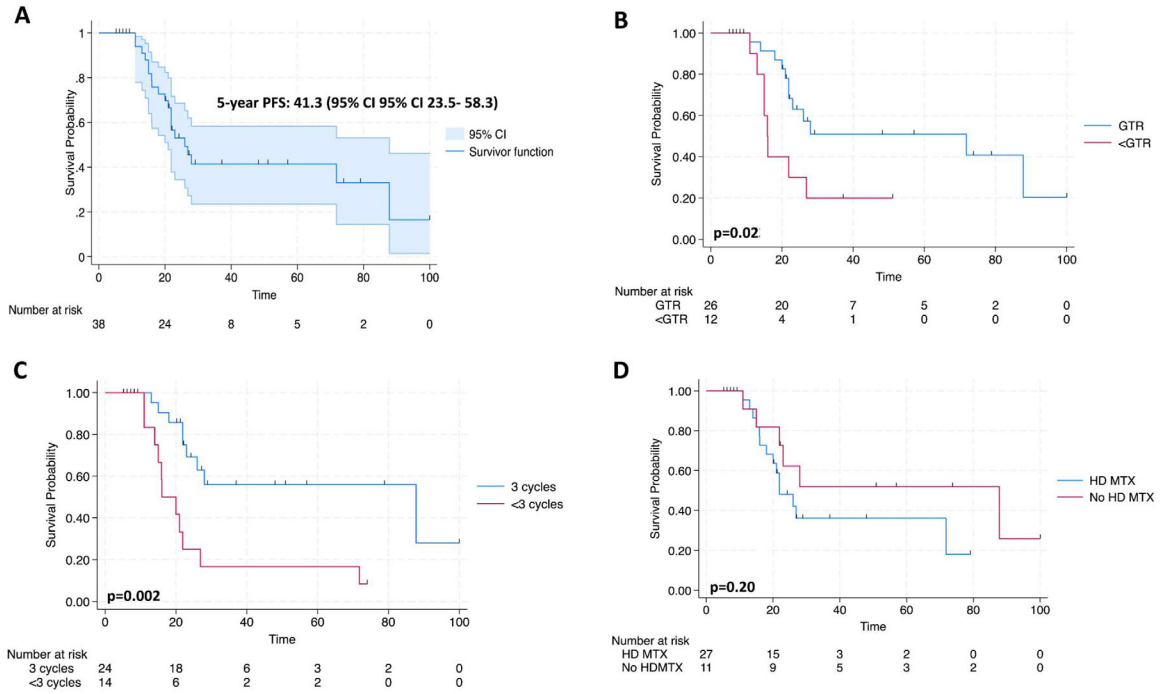

FIGURE 3 | Kaplan–Meier plot showing progression-free survival for the entire cohort (A), the extent of resection (B), the number of cycles of high-dose chemotherapy (HDC) (C), and the use of high-dose methotrexate during induction (D).

Fifteen patients (12 who did not relapse and three tested prior to relapse) had audiometric testing amenable to grading, including three Grade 1 or 0 (20%), three Grade 2 (20%), five Grade 3 (33.3%), and four Grade 4 (26.7%). Seven patients (46.6%) had hearing aids. Only three patients were tested after relapse (Grades 0, 1, and 2); one was reported wearing hearing aids.

Nine patients (23.7%) underwent neurocognitive testing, including six patients who did not relapse, one assessed prior to relapse, and two post relapses.

The seven patients who did not relapse or who were evaluated prior to relapse were evaluated at a median age of 5.4 years (range: 4.2–9.6) and a median time of 18.9 months from diagnosis (range: 15–78.9). Extracted full-scale intelligence quotient (FSIQ) on five of them ranged from 69 to 97 (median 81), while two other patients were reported to have mostly age-appropriate cognitive and intellectual skills.

Post-relapse neurocognitive evaluation was available only in two patients assessed at 5.7 and 5.2 years of age, 35.9 and 24.9 months from initial diagnosis, and 9 and 10 months from relapse. One patient who received 36 Gy CSI had an FSIQ of 77. The second patient, who received 23.4 Gy CSI, displayed overall widespread cognitive challenges.

4 | Discussion

Group 4 MB is predominantly observed in older children with a peak incidence typically between 5 and 13 years of age [13]. Therefore, most of these patients are treated with adjuvant CSI and chemotherapy. Data on the outcome of patients with Group 4 iMB treated on clinical trials with CSI-sparing strategies remain limited due to the small number of patients in this age group, and reported event-free survival varied widely from 13.3% to 83% [5, 6]. There is currently no available data for young patients treated with HDC strategies. The ACNS0334 trial included only two patients with Group 4 MB, and the recently closed HS 4 trial, which will report outcomes according to molecular subgrouping, is awaiting data maturation [7, 14]. We report here the largest cohort to date of young children with Group 4 iMB treated with an infant strategy based on HDC.

Our data confirmed patients with Group 4 MB present with late relapse (median time of 21.9 months from diagnosis; range: 5–99.8) compared to previous reports for patients with Group 3 and SHH (median time 11 months) [15–17]. In this cohort, the HDC and CSI-sparing approach was associated with a 52.6% relapse rate, and a 5-year PFS of 41.3% (95% CI: 23.5%–58.3%), a survival figure inferior to those reported in older children treated with adjuvant chemotherapy and CSI. In the ACNS0332 trial, children older than 3 years with HR Group 4 MB received 36 Gy adjuvant CSI and reached a 5-year event-free survival (EFS) of 65.6% (95% CI: 54.0%–76.6%) [18]. The ACNS 0331 trial led to a 5-year EFS of 86.7% (95% CI: 81.0%–92.4%) for patients with average-risk Group 4 MB. The subanalysis in this trial for younger patients with Group 4 MB (3–7 years old) indicated patients treated with lower dose of CSI (18 Gy) had significantly lower survival than those who received a standard dose (24 Gy) (5-year EFS of 77.2% vs. 97.1%, $p = 0.05$) [19], while in our cohort the 5-year PFS for SR patients was 45.7% (95% CI: 19.2%–60%). However, when placing this cohort in the context of infant brain tumor strategies, the PFS associated with this HDC compared favorably with the 5-year PFS of 13.3% reported for the 10 patients with Group 4 MB treated in the SJYC07 trial using conventional chemotherapy and adjuvant focal RT [6].

TABLE 3 | Prognostic factors for progression-free survival.

		Log-rank test		Univariate analysis		Multivariate analysis	
Variable	***N***	**5-year PFS (95% CI)**	***p*-value**	**Hazards ratio (95% CI)**	***p*-value**	**Adjusted hazard ratio (95% CI)**	***p*-value**
Sex							
Male (ref)	26	43.6% (21.3%–64.1%)	**0.56**				
Female	12	37.5% (10.9%–64.8%)		1.3 (0.52–3.4)	**0.56**	—	—
Age							
≤3 years (ref)	9	31.3% (4.8%–64.1%)	**0.82**				
>3 years	29	44.7% (24%–63.5%)		1.1 (0.40–3.1)	**0.82**	—	—
Surgery							
GTR (ref)	26	50.9% (27.3%–70.4%)	**0.02**				
<GTR	12	0		2.8 (1.10–7.1)	**0.03**	1.9 (0.71–5.2)	**0.20**
Metastasis							
M0 (ref)	24	35.9% (14.8%–57.7%)	**0.75**				
M+	14	48.6% (19.2%–73%)		1.2 (0.45–2.9)	**0.76**	—	—
Risk stratification							
SR (ref)	18	45.7% (19.2%–69%)	**0.17**				
HR	20	35.2% (13.3%–58.2%)		1.9 (0.75–4.7)	**0.18**	—	—
HD MTX during induction							
Yes (ref)	27	36.0% (15.9%–56.8%)	**0.20**				
No	11	51.9% (19.9%–76.7%)		1.9 (0.68–5.4)	**0.22**	—	—
HDC regimen[a]							
Carboplatin/Thiotepa (ref)	29	51.4% (28.9%–69.9%)	**0.002**				
Carboplatin/Thiotepa/Etoposide	8	0		4.2 (1.6–11.1)	**0.005**	—	—
Number of cycles of HDC							
3 cycles (ref)	24	55.9% (30.1%–75.5%)	**0.002**				
<3 cycles	14	16.7% (2.7%–41.3%)		3.9 (1.5–9.8)	**0.004**	3.2 (1.2–8.5)	**0.02**
Protocols (as per)[a]							
CCG 99703 (ref)	11	51.9% (19.9%–76.7%)	**0.008**				
ACNS 0334	18	52.1% (21.8%–75.6%)		1.1 (0.35–3.8)	**0.83**	—	—
Head Start	8	0		4.5 (1.3–14.8)	**0.01**	—	—

Abbreviations: GTR, gross total resection; HDC, high-dose chemotherapy; HD MTX, high-dose methotrexate; HR, high risk; M0, nonmetastatic; M+, metastatic; Ref, reference; SR, standard risk.

[a]Collinear variables with number of HDC cycles.

Given the rate of relapse observed, it is crucial to better define the subset of patients more likely to benefit from this approach. We identified that both GTR and the use of three cycles of HDC were associated with better PFS on univariate analysis, while the number of cycles of HDC was the only factor remaining significant in the multivariate analysis. The Head Start 4 protocol is investigating in a randomized manner the impact of three cycles of consolidation with carboplatin and thiotepa compared to one cycle of high-dose carboplatin, etoposide, and thiotepa for young patients with non-WNT non-SHH medulloblastoma. While this protocol will provide molecular characterization of the patients, it is unknown whether enough patients with Group 4 will be included in each arm to prospectively confirm our retrospective observation. Our cohort also provides insight into the impact of HD MTX during induction for Group 4 iMB. The ACNS0334 trial indicated a survival benefit with HD MTX for the Group 3 high-risk iMB, but no analysis could be performed for the two Group 4 MB enrolled on this study, and all patients enrolled on the HS4 trial received HD MTX during induction. We did not observe a significant survival difference associated with the use of HD MTX. However, SR patients accounted for 47.4% of our cohort, which may represent a confounding factor impacting the potential effect of HD MTX.

Although half of the patients experienced relapse, retrieval rate with salvage CSI delivered at a median dose of 36 Gy led to

a 5-year PRS of 60.3% (95% CI: 26.9%–82.3%). Erker et al. had previously reported a 3-year PRS of 84.1% (95% CI: 52%–96%) for 22 young children with relapsed Group 4 iMB. However, the patient characteristics, such as metastatic disease or rate of GTR, were different, precluding any comparison [15].

While such initial approach potentially commits SR patients to a higher dose of CSI at time of relapse than they would have received in an adjuvant setting, it is noticeable that almost half of patients (43.7%) underwent salvage CSI dose ≤23.4 Gy, without significant difference in their 5-year PRS: 75% (95% CI: 31.5%–93.1%) versus 72.9% (95% CI: 27.6%–92.5%) for those who received higher than 23.4 Gy. Age at relapse and pattern of relapse were not significantly associated with CSI dose, but we observed a significant association between CSI dose ≤23.4 Gy and the use of salvage chemotherapy and/or repeated surgery. However, we recognize treatment decisions to proceed to lower CSI dose may have been influenced by multiple factors, including the extent of resection at relapse, the choice of salvage chemotherapy, or the physician/family decision.

Overall, this approach of initial HDC and salvage CSI was associated with a 5-year OS of 72.7% (95% CI: 51.9%–85.7%). More clinically relevant, this strategy allowed more than half of the survivors (58.6%) to remain CSI-free, leading to a 5-year CSI-free OS of 69.7% (95% CI: 39.1%–87.1%) and a 5-year radiation-free overall survival of 75.9% (95% CI: 47.4%–90.3%).

We described a unique pattern of relapse and outcome for Group 4 iMB compared to Group 3 iMB [7]. It is unclear whether patients with Group 4 iMB should be treated similarly to those with Group 3 under the same umbrella of "non-WNT non-SHH iMB." This observation may be taken into consideration for the design of upcoming clinical trials.

Lastly, given a sizeable proportion of patients with initial localized disease presenting with local relapses (63.2%), the temptation may be to consolidate local control with initial adjuvant focal RT. However, with only two patients who received adjuvant fRT, we cannot comment on such an approach.

We described the neurocognitive and ototoxicity outcomes of 26.3% and 50% of the survivors, respectively. Albeit the limited number of patients, we observed a relatively preserved cognitive function, with a mean FSIQ of 86.5 in the patients spared from CSI. Nevertheless, infant strategies with HDC are heavily platinum-based, incorporating cisplatin during induction and high-dose carboplatin during consolidation. Using the SIOP Boston ototoxicity grading scale, we describe 60% of the assessed patients who developed Grade 3 or 4 ototoxicity prior to any CSI, and an additional 20% exhibiting Grade 2 ototoxicity, defined as a hearing loss greater than 20 dB at 4000 Hz and above. In young children, such high-frequency hearing impairment may significantly impact speech and language development, as well as academic achievement [20]. North American infant brain tumor strategies rely heavily on platinum, including a significant cumulative dose of cisplatin during induction, followed by a high dose of carboplatin for consolidation. Grade 3 and above ototoxicity by CTCAE criteria has not commonly been observed in the Headstart 3 and ACNS 0334 clinical trials (3.2% and 10.7%, respectively) [7, 9]. However, a retrospective study of young children with medulloblastoma treated with sequential HDC, using the Chang ototoxicity scale, indicated 45.5% of the evaluated patients had clinically significant hearing loss (Grade 2b and above), with 39% requiring hearing aids [21]. Hearing loss at this young age is known to affect speech acquisition and negatively impact academic outcomes [22]. While aiming at protecting neurocognition by avoiding cranial irradiation, these HDC strategies can also indirectly affect intellectual ability and social development through hearing impairment. Future prospective investigations of otoprotective agents like sodium thiosulfate will be important in this young age population as a potential intervention to mitigate the toxicity of HDC strategies [23].

This study has several limitations, including the absence of central review of the pathology, imaging, and molecular subgrouping. The molecular heterogeneity described within Group 4 MB, notably with the presence of additional alterations like MYC and MYCN amplification or within the methylation subgrouping are expected to impact outcome, highlighting the need to incorporate refined molecular classification in future therapeutic stratification [24]. Given the restricted sample size, we limited the multivariable Cox model to relevant and impactful covariates to ensure robust and stable estimates, acknowledging the possibility of minimal residual confounding from excluded variables that did not meaningfully impact hazard ratios.

While the retrospective nature of our study restricts generalization of findings, in absence of large number of young children with Group 4 iMB enrolled on prospective trials, we believe this sizeable cohort provides practical insights for treating physicians and families regarding expected outcome when considering upfront HDC and CSI-sparing approach, especially considering nearly 25% of the patients in our cohort were 3 years or younger at diagnosis.

5 | Conclusion

In this large cohort of Group 4 iMB, HDC and upfront CSI-sparing strategy led to a 5-year PFS of 41.3%. Best survival was observed in patients with initial GTR and those who received three cycles of consolidation. Salvage CSI was associated with a 5-year PRS of 60.5% and 5-year OS of 78.7%. The 5-year CSI-free overall survival for the entire cohort was 69.7%. This strategy represents an acceptable option to discuss with parents for young children with Group 4 iMB.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting information Supporting information