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CASE STUDY

Clinical, toxicity and long-term neurocognitive outcomes of first-line intensive chemotherapy in infant medulloblastoma: a single-center cohort study following AIEOP recommendations

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Abstract

Purpose The long-term neurocognitive impact of craniospinal irradiation (CSI) in young children with medulloblastoma (MB) has driven the development of alternative strategies aimed at improving survival while delaying or avoiding CSI.

Methods We retrospectively analyzed a cohort of patients under 5 years of age with MB treated at Bambino Gesù Children's Hospital between 2007 and 2023 with intensive chemotherapy regimens according to AIEOP recommendation. Clinical, radiological, histopathological, molecular, neurocognitive, and toxicity data were collected.

Results Among 42 patients under 5 years, 25 met inclusion criteria (median age 25.3 months, range 5.0–51.3). Histology included classic (52%), desmoplastic/nodular (20%), extensive nodularity (16%), and large cell/anaplastic (12%). SHH was the most common molecular subgroup (52%), followed by Group 3 (32%) and Group 4 (16%). At a median follow-up of 95.7 months, 68% were alive in complete remission. Two- and 5-year overall survival (OS) were 80.0% (95%CI: 58.4–91.1) and 65.9% (95%CI: 42.8–81.4); progression-free survival (PFS) was 68.0% (95%CI: 46.1–82.5) and 63.8% (95%CI: 41.8–79.2). Survival differed by risk group: low-risk patients achieved 100% OS and PFS, standard-risk intermediate, high-risk lowest. All experienced grade 3–4 hematological toxicity; late endocrine effects occurred in four patients, no other long-term toxicities reported. median IQ was stable from diagnosis (885.3) to last follow-up (8392.5.4).

Conclusion Our retrospective study of infants MB treated with first-line intensive chemotherapy shows encouraging survival rates. Importantly, neurocognitive function was preserved over time, supporting radiation-sparing strategies, and toxicity was manageable in all cases.

Keywords Medulloblastoma · Young children · Intensive chemotherapy · Survival · Neurocognitive outcome · Radiation-sparing strategies

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Introduction

Young children with medulloblastoma (MB) pose a major clinical challenge due to the vulnerability of the developing brain to neurotoxic treatments. Craniospinal irradiation (CSI) remains a cornerstone of therapy, but its long-term neurocognitive effects [1, 2] have prompted strategies aimed at improving survival while delaying or avoiding CSI. Early trials in the 1980s (e.g. UKCCSG) used conventional chemotherapy to defer radiotherapy but led to high progression rates and poor survival [3, 4]. More intensive approaches subsequently emerged, including chemotherapy followed by high-dose chemotherapy (HDC) with autologous stem cell rescue (ASCT), as in the HeadStart II protocols [5, 6], and regimens incorporating intraventricular or high-dose methotrexate (HIT-SKK92) [7, 8]. These strategies improved survival while minimizing early radiation exposure. Advances in radiation delivery, including intensity-modulated radiation therapy (IMRT) and proton beam therapy (PBT), further optimized dose distribution and spared healthy tissue [9]. Nevertheless, CSI is generally avoided in children under 3 years, with deferral beyond 5 years considered only in selected cases [10].

Molecular and histopathological studies have classified MB into four subgroups (WNT, SHH, Group 3, and Group 4) each with distinct biology and prognosis. In infants, most MBs are SHH or Group 3. Group 3 often exhibits MYC amplification, high metastatic risk, and poor prognosis, while SHH MB generally have better outcomes, though SUFU/PTCH1 mutations confer recurrence risk and worse prognosis. SHH MB are further divided into subtypes (SHH-1/β, SHH-2/ɣ, SHH-3/α, SHH-4/δ), with SHH-2 and SHH-4 linked to favorable outcomes [11]. These findings emphasize the importance of molecular stratification over age alone in guiding personalized, less toxic therapies [12–14].

This study evaluates intensive chemotherapy following AIEOP (Associazione Italiana di Ematologia e Oncologia Pediatrica) guidelines in infant MB, analyzing survival, clinical features, cognitive outcomes, and treatment-related toxicities.

Materials and methods

Patients

Data were retrospectively collected from 42 children (23 females, 19 males) diagnosed with MB before age 5 and treated at Bambino Gesù Children's Hospital between 2007 and 2023.

The inclusion criteria for this study were as follows: patients younger than 5 years at diagnosis, not eligible for active clinical trials, with histologically confirmed MB, who had received frontline treatment in accordance with the AIEOP recommendations [15].

Medical records were reviewed for demographics, neuroimaging, surgery, hydrocephalus management, histological/molecular data, cancer predisposition syndromes (CPS), chemotherapy details, and neuropsychological assessments. Data on outcomes were also collected.

The study was approved by the Institutional Review Board of Bambino Gesù Children's Hospital and conducted in accordance with the Helsinki Declaration.

Radiological assessment: diagnosis and treatment response

All patients eligible for the analysis underwent a magnetic resonance imaging (MRI) protocol on a 3 Tesla scanner (Siemens, Erlangen, Germany) under sedation. The protocol involved study of the brain and spine in the same session with the following sequences: T2 TSE (slice thickness 3 mm), DWI with ADC maps (b = 0,1000, 3 mm), SWI (1,5 mm) and volumetric FLAIR (1 mm) and T1 SPACE (< 1 mm). The study of the spine was performed with sagittal T1 and T2 TSE (2 mm) and axial T1 (2 mm).

Regarding MRI analysis, two neuroradiologists evaluated in consensus the conventional tumor parameters according to RAPNO (Response Evaluation in Pediatric Neuro-Oncology) guidelines for MB and leptomeningeal seeding tumors [16].

Histopathological and molecular characterization

All cases were classified according to the 2021 WHO pediatric brain tumor criteria [17]. DNA methylation profiling was performed in all cases. Details of immunohistochemical and molecular analyses are provided in the supplementary materials (Suppl 1).

Surgery

Maximal safe microsurgical resection, whenever feasible, was performed at the time of first diagnosis by occipital craniotomy in prone position. Instead, biopsy was considered if resection of the principal posterior fossa lesion would not significantly reduce local mass effect and disease load due to massively disseminated disease. Our institutional policy included navigation assistance and intraoperative monitoring in all cases. Symptomatic hydrocephalus was treated before surgical resection by endoscopic third ventriculostomy (ETV). Ventriculo-peritoneal (VP) shunt was considered only after documented failure of ETV or in presence of documented cisternal blockage by disseminated disease. If

extensive spinal dissemination was present an intraventricular access device was positioned to overcome the need for therapeutic spinal taps.

Treatment

All 25 patients included in the study received chemotherapy regimens based on the AIEOP indications [15]. It consisted of three courses of chemotherapy: methotrexate (8000 mg/m^2) and vincristine (1,5 mg/m^2) on day 1, etoposide (2400 mg/m^2) on day 8, cyclophosphamide (4000 mg/m^2) and vincristine (1.5 mg/m^2) on day 28. The treatment was continued four weeks after the end of conventional chemotherapy (or upon hematologic recovery) with two cycles of high-dose chemotherapy with Thiotepa 900 mg/m^2 and ASCT. If residual disease and/or metastases persist after two high-dose chemotherapy cycles and the patient is not eligible for second-look surgery, or if residual disease persists after a second surgery, a third cycle of high-dose chemotherapy with thiotepa (750 mg/m²) and carboplatin (1 g/m²) was planned [15] (Supll 2). The same treatment regimen was applied to all patients, regardless of risk group.

As second-line treatment, chemotherapy and/or radiation therapy were administered at relapse or progression. The minimum age at which CSI was allowed was 48 months. CSI consisted of a dose of 36 Gy, with a boost of 18 Gy to the posterior fossa and disease sites, for a total dose of 54 Gy. PBT became available in Italy starting in June 2015. In PBT, a uniform vertebral dose was delivered, with the Clinical Target Volume including the whole brain (cribriform plate and proximal optic nerves) and the entire spine (subarachnoid space, vertebral body, nerve roots) down to the thecal sac end (S2–S3).

Neurocognitive assessment

Cognitive assessments were conducted at diagnosis, one year after the end of treatment, and at last follow-up for patients who were still alive. Age-appropriate, validated tools were used, including the Griffiths Mental Development Scales (GMDS) and the Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV) [18].

The GMDS evaluates overall development in children from birth to 8 years across five domains: gross motor skills, personal-social behavior, language development, fine motor coordination, and performance abilities [19]. The WISC-IV provides a full-scale IQ and four composite indices; for this study, only the overall cognitive level was considered [20]. All children underwent rehabilitation once or twice a week. Depending on the profile that emerged during assessment, the training focused on supporting executive functions, visuospatial processing, eye-hand coordination, sensorimotor functions, and language.

Toxicity evaluation

All patients underwent regular follow-up during and after treatment, per institutional protocols. Hematologic toxicity was monitored throughout therapy and follow-up. Endocrine evaluations (ACTH, Cortisol, IGF-1, GH, FSH, LH, TSH, FT4, testosterone, 17β-estradiol) were performed at baseline and every 6 months from the end of treatment. Cardiac function (ECG, echocardiogram, clinical examination), pulmonary function (spirometry ± DLCO), and audiometry were assessed at baseline and at 6-month intervals up to 24 months post-treatment. Thereafter, assessments were performed annually for patients who were still alive. Toxicities were graded according to CTCAE v5.0 criteria [21].

Statistical analysis

Data entry and cleaning processes were conducted using Microsoft Excel. Descriptive statistics were reported as counts and percentages for categorical variables and median and interquartile range (IQR) for continuous variables.

Overall survival (OS) and progression-free survival (PFS) were calculated using the Kaplan-Meier method. OS was defined as the time from the date of diagnosis to death from any cause or last follow-up. PFS was defined as the time from the date of diagnosis to the date of relapsed/progressive disease or death from any cause. Patients without documented progression or death were censored at the date of last follow-up.

Survival outcomes were compared according to histology, molecular subgroups, metastasis, extent of resection, CPS and Cerebellar Mutism Syndrome (CMS). Moreover, patients were stratified into three risk groups [22]: low (LR), standard (SR) and high risk (HR), to assess the correlation between risk category and survival outcomes.

Associations between relapse/progression and clinical, pathological and molecular variables were assessed using Fisher's exact test. The Logrank non-parametric test for comparison of survival distributions was used to compare survival differences between groups. The alpha risk was set to 5.0%.

For the statistical analysis, GraphPad Prism version 10.4.1 (GraphPad Software, San Diego, CA, 2023) was used.

Results

During the 16-year period, we identified a total of 42 patients with infant MB, with a median age at diagnosis of 31.7 months (range 5.1–58.0). Seventeen patients were excluded because they had received radiotherapy as part of first-line therapy, were enrolled in clinical trials, or had not been treated according to AIEOP recommendations. Finally, twenty-five patients matched the inclusion criteria and were enrolled in the study, including 12 male and a 13 female with a median age at diagnosis of 25.3 months (range 5.0–51.3 months). 44% of patient were metastatic at diagnosis. Patient' characteristics are detailed in Table 1.

Surgical management

At diagnosis, 17/25 patients had hydrocephalus; 15 underwent endoscopic third ventriculostomy (ETV), one received a VP shunt, and one a ventricular access device. All patients had surgery: 15 gross total resections (GTR), 2 near-total (NTR), 6 subtotal (STR), and 2 biopsies. One patient, operated at an external center, experienced severe postoperative complications requiring tracheostomy and gastrostomy; two had transient neurological deficits that improved. CMS occurred in 5 of 18 evaluable patients and was fully reversible.

Pathology and molecular findings

At histological examination 13/25 cases were classified as classic (CL), 5/25 desmoplastic nodular (DN), 4/25 with extensive nodularity (MBEN), and 3/25 large cell/anaplastic (LCA). DNA methylation profile highlighted the SHH subgroup as the most representative (13/25) with TP53 status wild type in all cases, followed by group 3 (8/25) and group 4 (4/25). MYC amplification was detected in only 3 cases of group 3 MB.

Cancer predisposition syndrome

Seven patients carried likely pathogenic or pathogenic variants. P5 and P20 were diagnosed with Gorlin syndrome, both carrying heterozygous SUFU variants: c.16delC (P5) and c.364delT (P20), the latter with a maternal history of basal cell carcinomas. P6 had a likely pathogenic POLE variant (c.2584_2585delGA); her family history included breast cancer. P13 carried a GPR161 variant (c.714dupG) inherited from her father, with limited cancer history but a report of macrocrania in a paternal uncle. P18 was diagnosed with Tatton-Brown-Rahman syndrome due to a DNMT3A variant (c.427 C>T), inherited from the father. P23 had Cowden syndrome with a de novo PTEN alteration (c.79T>A) and clinical features including MB, intestinal polyposis, and macrocrania. P24 carried biallelic MUTYH variants (c.1353_1355delCCT and c.228G>T), with familial history of gastrointestinal and gynecological cancers. Molecular and histological details are reported in supplementary table (Suppl 3).

Survival and outcome

Median OS for the whole population was 58 months (range 8.7-173.9). Seventeen out of 25 patients (68%) are alive and in complete remission with a median follow-up of 95.7 months (range 28.2-173.9). Three patients progressed during first-line treatment, and five relapsed after achieving complete remission at a median time of 7.6 months (range 2-24.2) upon completion of therapy. Among the patients who experienced relapse or progression, 7 out of 8 (87.5%) had the CL/LCA histotype ($p=0.28$). Regarding molecular subgroups, 50% were classified as Group 3, while the remaining 50% were evenly distributed between SHH and Group 4 ($p=0.13$). Metastatic disease at diagnosis was present in 37.5% of relapsed/progressed patients and 50% of non-relapsed/progressed patients ($p=0.67$). Chemotherapy was administered in all but one of the relapsed/progressed cases. Four patients received CSI: 2 with standard radiotherapy and 2 with PBT. Of the relapsed/progressed patients, only one remained alive and he is the patient re-irradiated with PBT. All other patients died after a median of 5.2 months (range 1–39 months) after relapse/progression. One patient died of treatment-related toxicity.

At 2 years, OS was 80.0% (95%CI: 58.4–91.1) and PFS was 68.0% (95%CI: 46.1–82.5); at 5 years, OS was 65.9% (95%CI: 42.8–81.4) and PFS was 63.8% (95%CI: 41.8–79.2) (Fig. 1a-b).

When evaluating the outcome of patients with DN/MBEN subgroup compared to CL/LCA, it can be observed that, patients with DN/MBEN show higher 2- and 5-year OS ($p=0.096$) and PFS ($p=0.04$) compared to those with CL/LCA (Fig. 2a-b). Patients with MBEN showed low relapse and mortality rate (11.1%), compared to CL/LCA (43.8%) ($p=0.182$). When analyzed by molecular subgroup, patients with SHH MB showed the most favorable OS ($p=0.09$) and PFS ($p=0.04$) than G3 and G4 (Fig. 2c-d). Relapse were respectively 15.4%, 50.0%, and 50.0% in SHH, G3 and G4 ($p=0.179$); mortality was 15.4%, 37.5% and 75.0% ($p=0.009$).

Moreover, GTR/NTR resections was associated with better outcomes than STR/biopsy ($p=0.37$) and localized disease showed a favourable trend in comparison with metastatic disease ($p=0.24$) (Fig. 3a-b). Patients who developed CMS had worse outcomes than those without CMS ($p=0.49$) (Fig. 3c). All seven patients with CPS and infant

Table 1 Patient's characteristics

Pt	Sex	Age at diagnosis (months)	Histotype	Molecular subgroup	MyC Status	Metastasis	Hydrocephalus Treatment	Surgery	CMS	Disease Status at stop therapy	Progression/Relapse	2 nd line treatment	Patient status at last follow-up	OS (m)
1	M	28	CL	SHH-A	NAmp	Y	ETV	STR	NO	CR	N		A	139.3
2	M	24	MBEN	SHH-B	NAmp	N	ETV	NTR	NO	CR	N		A	95.8
3	M	22	LCA	G3	NAmp	N	ETV	GTR	YES	CR	N		A	166.1
4	F	33	DNMB	SHH-B	NAmp	N	NA	GTR	NO	CR	Y	CT	D	47.8
5	M	46	CL	SHH-B	NAmp	Y	NA	Biopsy	NO	CR	N		A	58.0
6	F	14	CL	G3	NAmp	Y	ETV	GTR	NA	CR	N		A	64.7
7	F	43	CL	G4	NA	N	ETV	GTR	NO	CR	Y	CT, RT	D	11.6
8	M	20	CL	G4	NAmp	Y	VPshunt	STR	NA	NA	NA	NA	D	10.7
9	M	44	CL	G3	NAmp	Y	ETV	GTR	YES	CR	N		A	28.2
10	F	43	LCA	G3	Amp	Y	ETV	GTR	NA	PD	Y	RT, HD-CT	D	9.1
11	F	58	CL	G3	Amp	Y	ETV	Biopsy	NA	CR	Y	CT, IT	D	24.1
12	M	18	CL	G4	NAmp	N	ETV	STR	YES	CR	N		A	134.3
13	F	30	DNMB	SHH-B	NAmp	N	Rickham	NTR	NO	CR	N		A	110.0
14	M	26	CL	SHH-A	NA	Y	ETV	STR	YES	PD	Y	NO	D	8.7
15	M	5	MBEN	SHH-B	NAmp	Y	NA	GTR	NA	CR	N		A	173.9
16	F	19	CL	G3	NAmp	N	ETV	GTR	NA	CR	N		A	33.7
17	F	21	MBEN	SHH-B	NAmp	Y	ETV	GTR	NO	CR	N		A	117.2
18	M	29	DNMB	SHH-B	NAmp	N	NA	STR	NO	CR	N		A	33.6
19	M	38	CL	G3	NAmp	N	ETV	GTR	NO	CR	Y	CT, PBT	A	125.9
20	F	24	DNMB	SHH-A	NAmp	N	NA	GTR	NO	CR	N		A	29.7
21	F	52	LCA	G4	NAmp	N	ETV	GTR	NO	CR	Y	CT, IO, PBT	D	54.2
22	F	18	CL	SHH-A	NAmp	N	ETV	STR	NO	CR	N		A	115.6
23	M	15	MBEN	SHH-B	NAmp	N	NA	GTR	NA	CR	N		A	78.9
24	F	19	DNMB	SHH-B	NAmp	N	NA	GTR	NO	CR	N		A	64.8
25	F	28	CL	G3	Amp	Y	NA	GTR	YES	PD	Y	CT, IO	D	11.0

M: male; F: female; CL: classic; DN desmoplastic nodular; MBEN: extensive nodularity; LCA: large cells/anaplastic; Amp: amplified; NAmp: not amplified; ETV: Endoscopic Third Ventriculostomy; VP: Ventriculo-Peritoneal; GTR: Gross Total Resection; NTR: Near Total Resection; STR: Subtotal Resection; CMS: Cerebellar Mutism Syndrome; CR: complete remission; PD: progressive disease; CT: chemotherapy; HD-CT: high-dose chemotherapy; RT: radiotherapy; PBT: protontherapy; IO: immunotherapy; IT intrathecal therapy; A: alive; D: dead. NA: not available

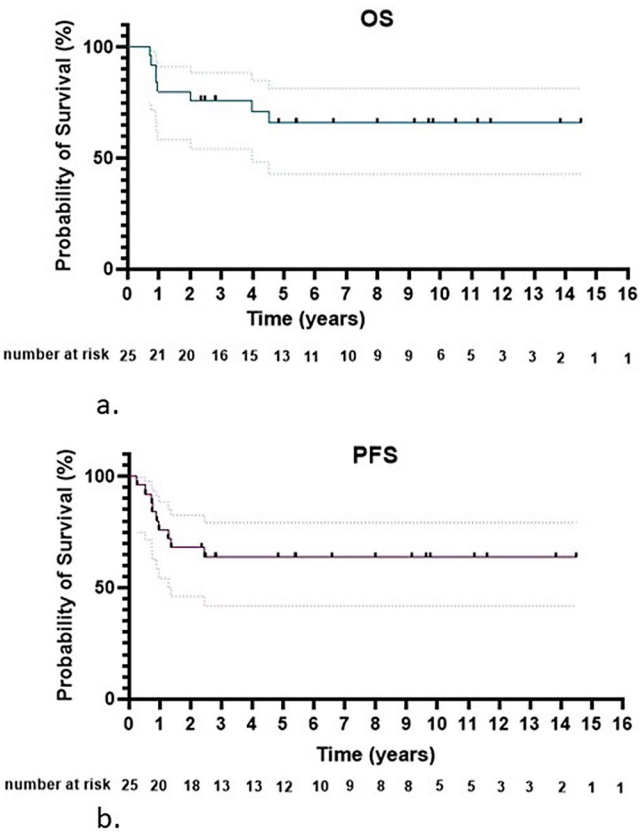

Fig. 1 Kaplan Meier survival analysis of 25 evaluable patients: (**a**) OS ± 95% CI, (**b**) PFS ± 95% CI

MB were alive at the last follow-up with a median survival of 64.7 months (range, 29.7–110 months).

When patients were stratified by risk group, 2-year and 5-year OS rates were 100% for the LR group, 87.5% (95%CI 38.7–98.1) and 72.9% (95%CI 27.6–92.5) for the SR group, and 63.6% (95%CI 29.7–84.5) and 43.6% (95%CI 14.7–69.9) for the HR group ($p = 0.05$). Corresponding 2-year and 5-year PFS rates were 100% for LR, 62.5% (95%CI 22.9–86.1) for SR at both timepoints, 54.5% (95%CI 22.9–78) and 43.6% (95%CI 14.7–69.9) for HR ($p = 0.1$) (Fig. 2e-f).

Cognitive assessment

Median IQ at diagnosis was 88 (IQR 72.5-103.5), 82 (IQR 65.5-92.5) at one year from diagnosis and 92.5 (IQR68.25-104.75) at the last follow-up, without difference between different time points (Table 2). The median time of last IQ assessment in relation to tumor diagnosis was 94.8 months (range 21.1- 169.4). Importantly, even in the single surviving patient who underwent CSI with PBT, no relevant change in IQ was observed (score 85 at the last assessment, 110 months after treatment completion).

Toxicity

In our cohort, all patients experienced hematological toxicity. In particular, grade 3–4 neutropenia was detected in all 25 patients. Grade 3–4 thrombocytopenia and grade 3 anemia were assessed in 18 and 11 patients, respectively. One patient died of septic shock during the third cycle of high-dose chemotherapy. Twenty-two patients experienced transient elevated transaminase levels, although only half of them showed a moderate-severe grade toxicity.

Regarding endocrinological toxicities, the majority of patients (21 out of 25) did not show any hormonal impairment during follow-up evaluations. Four out of 25 patients presented endocrinological sequelae, including: growth hormone deficiency associated with delayed puberty (1/4) and hypothyroidism (1/4), delayed pubertal development requiring hormone replacement therapy (1/4), and suspected primary ovarian insufficiency currently under investigation (1/4). Median time of onset of endocrinological sequelae was 55.5 months after the end of therapy (range 37–91 months). The patient with growth retardation and hypothyroidism had been treated with PBT, while the other three had not received radiation therapy.

No audiological, renal, cardiac or pulmonary toxicities have been reported.

Discussion

This retrospective study describes the clinical features, treatment outcomes, and toxicities in patients under 5 years of age with MB treated with first-line intensive chemotherapy according to AIEOP recommendations. In our cohort, the 2- and 5-year OS and PFS rates were encouraging, although derived from a relatively small population. No statistically significant OS differences were observed across histotype, molecular subgroup, disease status, or extent of resection, although trends suggested better outcomes with DN/MBEN subtypes, SHH subgroup, more extensive resections, and localized disease. PFS, however, was statistically significantly higher for DN/MBEN and SHH patients. These findings, despite the small sample size, are clinically relevant and consistent with previous literature [22]. Recently, considerable attention has been given to stratifying patients into risk groups to better tailor treatment intensity and optimize outcomes [22, 23]. Our results confirmed its prognostic value: low-risk patients achieved excellent outcomes, standard-risk had intermediate results, and high-risk experienced the poorest survival [22].

Among non-metastatic DN/MBEN MB-SHH cases, the highest reported 5-year PFS (93%) was achieved in the German HIT 2000 trial combining intraventricular and

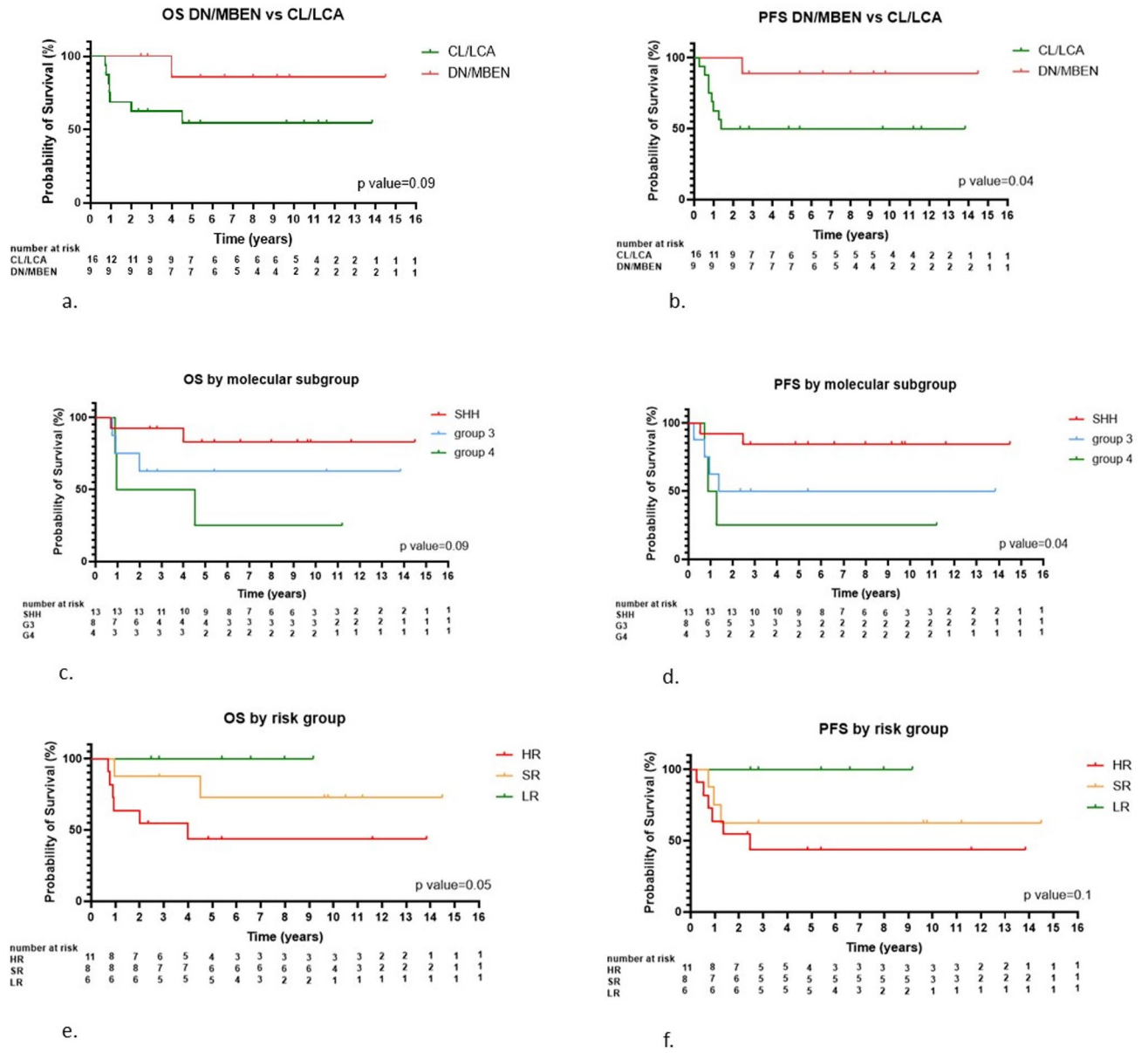

Fig. 2 Kaplan Meier survival analysis of 25 evaluable patients (**a**) OS dependent on histological subtype, (**b**) PFS dependent on histological subtype, (**c**) OS dependent on molecular subtype, (**d**) PFS dependent on molecular subtype, (**e**) OS dependent on risk group (**f**) PFS dependent on risk group

high-dose intravenous methotrexate with conventional chemotherapy [7], a result similar to what we observed in our cohort. The CCG-99,703 trial reported 78.6% 5-year PFS with conventional chemotherapy followed by repeated myeloablative cycles [24]. In contrast, ACNS1221 and SJYC07, which omitted intraventricular methotrexate or HDC, reported PFS of 66.7% and 74.5%, respectively [10, 25], underscoring the need for therapy intensification and local control. Finally, for DN/MBEN MB-SHH tumors, associated with improved survival, the standard of care includes autologous transplant (HeadStart, CCG-99703) or intraventricular methotrexate with systemic chemotherapy [6, 24], and radiotherapy can often be safely omitted [6, 25].

In contrast, infants with classic or LCA histology (predominantly non-WNT/non-SHH Group 3) continue to have poor prognosis, as also observed in our study. In the HIT-SKK'92 trial, patients with classic histology had 5-year PFS and OS of 34 ± 10% and 41 ± 11%, compared with 85 ± 8% and 95 ± 5% for DN tumors [8]. The UKCCSG 9204 study reported 5-year OS of 33.3% for classic and 0% for LCA variants [4]. Similarly, in HIT2000, DN/MBEN tumors had superior 5-year EFS/OS (95 ± 5% / 100 ± 0%) compared with classic MB (30 ± 11% / 68 ± 10%) [26]. In the

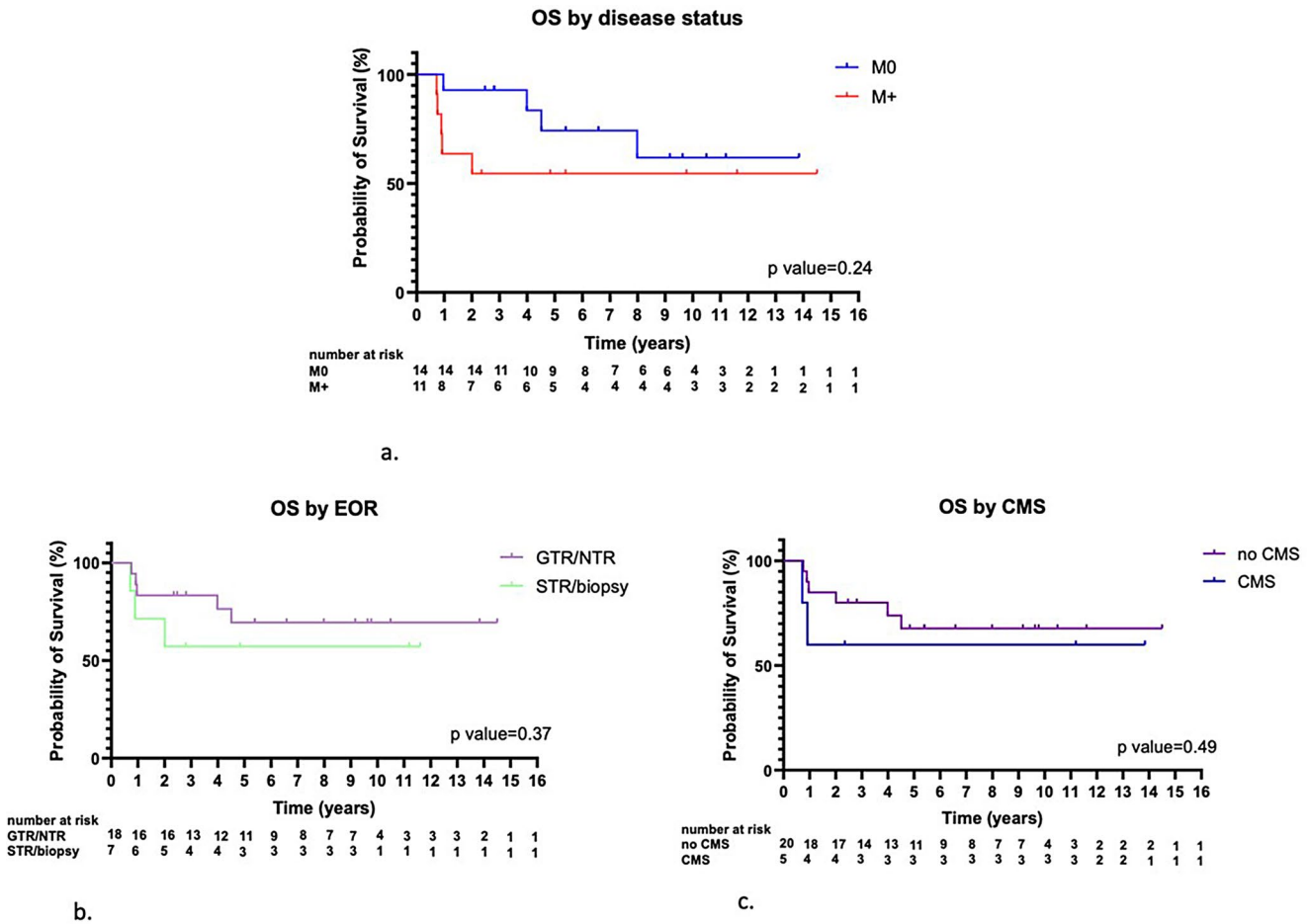

Fig. 3 Kaplan Meier survival analysis of patients (**a**) OS dependent on disease status, (**b**) OS dependent on extent of resection, (**c**) OS dependent on CMS

Table 2 IQ scores at diagnosis, 1 year post-diagnosis, and at last follow-up

Variable	Number of patients	Mean (SD) Count (%)	95% CI	Min Max	IQR	Median
IQ diagnosis	19	85.32 (24.43)	73.54–97.09	40 130	72.5-103.5	88
IQ 1 year post-diagnosis	19	78.47 (21.74)	67.99–88.95	30 115	65.5–92.5	82
IQ last follow-up	10	83.35 (28.12)	63.23-103.47	22.5 111	68.25-104.75	92.5

Children's Oncology Group P9934 study, 4-year EFS and OS for DN tumors were 58 ± 8% and 79 ± 7%, versus 23 ± 12% and 31 ± 16% for non-DN/MBEN [27]. In SJYC07, non-SHH patients had 5-year EFS and OS of 10.6% and 50.5% [10]. Head Start I/II showed 5-year EFS and OS of 42% and 67% [28], while CCG-99,703 reported 50.5 ± 11.8% EFS and 60.6 ± 11.6% OS for non-DN tumors [24]. Head Start III reported 5-year EFS/OS of 26.6 ± 6% / 53 ± 7% for classic and 38 ± 13% / 46 ± 14% for LCA, with radiation-free EFS of 21 ± 5% [6].

In 2016, Lafay-Cousin and collegeus reported their retrospective study of 53 young children with MB treated with sequential high-dose chemotherapy, with a 5-year EFS of 69.6% and OS of 76.1%, consistent with our findings. SHH tumors, including nodular desmoplastic and a subset of classic histology, achieved the most favorable outcomes (5-year EFS of 86%), whereas group 3 tumors had significantly poorer results (49%; 46% without radiotherapy). As expected, patients with metastatic disease experienced the worst OS [29].

Our 5-year PFS and OS curves were nearly overlapping, emphasizing relapse as the main cause of mortality. All but one relapsed/progressed patient died, with a median post-relapse/progression survival of 5.2 months, including three

of the four patients who received CSI. This indicates that salvage therapy, even when including CSI, rarely rescues patients and is associated with additional morbidity [30].

In our cohort, 20% of patients had germline cancer-predisposing variants, higher than the usual 8–10% [31], highlighting the need to minimize radiotherapy due to elevated secondary malignancy risk. In our series, all patients with CPS are alive at last follow-up and have not developed secondary neoplasms.

Neurocognitive outcomes were reassuring: median IQ at diagnosis (88.3 IQR 72.5-103.5) remained stable over time. The only long-term survivor who received proton CSI showed no neurocognitive impairment, supporting the feasibility of radiation-sparing strategies. These results are consistent with previous studies reporting better cognitive outcomes following chemotherapy-based, radiation-minimizing treatments [32, 33].

Hematological toxicity was as expected [10], with all patients experiencing grade 3–4 neutropenia and frequent thrombocytopenia and anemia; one patient with multiple comorbidities and severe postoperative complications requiringtracheostomy and gastrostomy, died of septic shock during third ASCT conditioning. Endocrinological toxicity occurred in four patients, mainly presenting as delayed growth or puberty, with only one having received CSI PBT. No other significant toxicities were reported.

This study has several limitations. First, the rarity of the disease resulted in a small overall cohort and even smaller subgroups, which limits the statistical power and the robustness of subgroup analyses. Second, 17 patients were excluded from the original cohort, which may introduce selection bias. Finally, this is a single-center study, which may reduce the generalizability of the findings. Validation in larger, multicenter cohorts is warranted.

Ongoing research is exploring novel strategies such as immunotherapy. Donovan et al. tested locoregional CAR T cells targeting EPHA2, HER2, IL-13, showing efficacy in metastatic Group 3 MB mouse models [34]. Ciccone et al. demonstrated that systemic CAR.GD2 T-cell administration inhibited tumor growth and prolonged OS in orthotopic models [35].

Conclusions

Medulloblastoma in young children poses significant treatment challenges due to the risks of neurotoxicity from CSI. Our retrospective study of infants with MB treated with intensive first-line chemotherapy shows encouraging survival rates. Importantly, toxicities were manageable and neurocognitive function was preserved over time, supporting radiation-sparing strategies. These findings support chemotherapy-based approaches and underscore the need for collaborative studies. Ongoing research in targeted and immunotherapies is essential to further enhance survival and quality of life.

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Author contributions GDB, ACar, AM, contributed to the study conception and design. Material preparation and data collection were performed by GDB, VDR, ACac, ALS, LC, CD, ADS, GA, SC, EM, IG, SR, GSC, SV, AC. Data analysis was performed by GDB. The first draft of the manuscript was written by GDB and VDR; all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability All data generated or analysed during this study are included in the published article, its tables, and the supplementary material.

Declarations

Ethics approval The study was conducted by the Declaration of Helsinki and approved by the Institutional Review Board of Bambino Gesù Children's. Code of Approval: RAP-2025-002.

Competing interests The authors declare no competing interests.

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