Molecular Classification Improves Therapeutic Options for Infants and Young Children With Medulloblastoma

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ABSTRACT

Medulloblastoma in infants and young children is a major challenge to treat because craniospinal irradiation (CSI), a cornerstone of therapy for older children, is disproportionately damaging to very young children. As a result, trials have attempted to delay, omit, and replace this therapy. Although success has been limited, the approach has not been a complete failure. In fact, this approach has cured a significant number of children with medulloblastoma. However, many children have endured intensive regimens of chemotherapy only to experience relapse and undergo salvage treatment with CSI, often at higher doses and with worse morbidity than they would have initially experienced. Recent advancements in molecular diagnostics have proven that response to therapy is biologically driven. Medulloblastoma in infants and young children is divided into 2 molecular groups: Sonic Hedgehog (SHH) and group 3 (G3). Both are chemotherapy-sensitive, but only the SHH medulloblastomas are reliably cured with chemotherapy alone. Moreover, SHH can be molecularly parsed into 2 groups: SHH-1 and SHH-2, with SHH-2 showing higher cure rates with less intensive chemotherapy and SHH-1 requiring more intensive regimens. G3 medulloblastoma, on the other hand, has a near universal relapse rate after chemotherapy-only regimens. This predictability represents a significant breakthrough and affords oncologists the ability to properly risk-stratify therapy in such a way that the most curative and least toxic therapy is selected. This review examines the treatment of medulloblastoma in infants and young children, discusses the molecular advancements, and proposes how to use this information to structure the future management of this disease.

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Medulloblastoma is one of the most common malignant central nervous system tumors of childhood.[1,2] Standard therapy is multimodal and combines maximal safe surgical resection with risk-adapted craniospinal irradiation (CSI) and chemotherapy based on metastatic stage and extent of resection.[3–7] This therapy is highly effective and cures >75% of patients.[4] However, this treatment is disproportionately damaging to the growth and development of very young children. In particular, CSI induces irreparable and progressive damage to neurocognition, growth, and development in a dose-dependent manner that is inversely proportional to age. To this effect, therapeutic strategies for very young children with medulloblastoma have concentrated on CSI avoidance. Unforgivingly, this deliberate omission of CSI has resulted in worse outcomes, with a progression-free survival (PFS) rate of 30% to 50% and an overall survival (OS) rate of 60% to 65%, which is contingent on the reinstatement of CSI.[8]

Given that the CSI-induced damage occurs across a continuum rather than at an exact age, there is a debate among neuro-oncologists regarding the age at which CSI should be used in frontline therapy. To distinguish patients who do not receive up-front CSI from those who do, the term "infant" has been used. However, the upper age limit for this term has remained ambiguous, mainly because different thresholds have been used in different clinical trials. Despite these discrepancies, all seem to agree that the morbidity in patients aged <3 years outweighs the benefits, and these patients are treated with CSI-sparing strategies. However, in various contexts and trials, neuro-oncologists have included patients up to 10 years old in these strategies.[9] For this review, we have elected to focus on patients diagnosed at <6 years of age and, for consistency, we will use the term "infants" for those aged <3 years and "young children" for those aged 3 to 6 years.

Our objective is to discuss the current knowledge of medulloblastoma in infants and young children. This review describes the treatment protocols and studies that have defined the management of this population. Furthermore, we review the newest molecular findings and

discuss how these are changing our understanding of age-related demographics, prognosis, and survival, and are ultimately leading to new risk stratification models for therapy.

Historical Studies Reveal a Vulnerable Young Age Group and a Histologic Subtext

Before the 1980s, all children, regardless of age at diagnosis, were treated with surgical resection followed by CSI consisting of a minimum dose of 36 Gy.[10] Studies performed on survivors revealed that cure came at a significant cost: >85% developed moderate to severe neurocognitive deficits (moderate: IQ 70–90; severe: IQ <70), and approximately 60% developed neuroendocrine deficiencies.[11–14] Moreover, these studies showed that younger age was associated with a higher severity of deficits, motivating reduced-dose CSI (23.4 Gy) in the older patients with nonmetastatic (M0) disease and radiation avoidance in the younger population.

At first, radiation avoidance began as a delaying strategy to bridge the patient to an age at which CSI could be administered with more acceptable neurocognitive-related comorbidities (generally 3 years old).[15–18] One of the first trials was POG-1, in which infants were postoperatively treated with systemic chemotherapy followed by CSI at 3 years of age. Those with gross total resection (GTR) and M0 disease had an OS rate of 69% when treated with 24 Gy of CSI. Patients diagnosed with subtotal resections and/or metastatic (M+) disease had an OS rate of 32%, even when treated with the higher dose of 36 Gy CSI.[18–22] Similarly, the German Society for Paediatric Oncology and Haematology designed the HIT-SKK'87 protocol to evaluate the efficacy of postoperative chemotherapy followed by CSI at progression or 36 months of age. The 10-year PFS and OS rates were 48.3% ± 9.3% and 55.2% ± 9.3%, respectively, with metastatic status serving as a strong prognostic indicator of clinical outcome.[21]

These trials established that chemotherapy could delay radiation, but despite a promising survival range, the surviving population continued to have unacceptably low IQ.[23] In HIT-SKK'87, the mean IQ of patients at 6 years postdiagnosis was significantly lower than for age-matched healthy controls (IQ: 77.7 ± 7.2 vs 104.1 ± 11.3).[21] Similarly, the median IQ of survivors of infant medulloblastoma treated at St. Jude Children's Research Hospital with radiation-delaying strategies decreased from a baseline of 88 (range, 50–111) to 62 (range, 44–86).[22] Thus, radiation sparing, or avoidance approach, was tested in subsequent trials (Table 1).

One of the first avoidance trials was CCG-9921, which used a more intensive chemotherapy regimen and sought to eliminate CSI if patients were disease-free at the end of the planned chemotherapy. With a 5-year event-free survival (EFS) of 41% in patients with GTR and M0 disease, the idea that intensified chemotherapy could replace CSI gained attention and a series of trials ensued.[20] In general, 3 approaches to replace CSI were used: (1) high-dose (myeloablative) chemotherapy with autologous stem cell rescue (HDC-AuSCR)[9,24–26]; (2) intraventricular methotrexate with systemic chemotherapy (IVT-MTX)[27,28]; and (3) focal radiation therapy (RT) combined with systemic chemotherapy.[29,30] In the HDC-AuSCR category were the Head Start (I, II, and III)[9,24] and CCG-99703[26] protocols; IVT-MTX was used in the HIT-SKK'92[27] and HIT-SKK 2000[28] protocols; and focal RT was used by P9934[29] and PBTC-001.[31] For the most part, the results were similar and the 5-year PFS ranged between 60% and 70% for patients with GTR and M0 disease, but dipped into the 25% to 35% range for those with metastatic disease. However, these therapies had their drawbacks. Those who received focal RT often experienced a metastatic relapse.[29,30] The toxicity of HDC-AuSCR was responsible for approximately 10% to 14% of therapy-related deaths.[24,25] Leukoencephalopathic changes were seen in patients receiving IVT-MTX.[17,27,32,33] Hearing impairments were widely prevalent from chemotherapy.[34] Most distressing of all, 40% to 50% of patients who experienced relapse had to receive salvage treatment with CSI. Consequently, almost half the patients were exposed to both the heightened toxicity of an intensified chemotherapy regimen and the same CSI that these therapies were designed to avoid.

Still one of the most important findings from these CSI avoidance studies was that survival was not just associated with clinical risk (ie, metastatic disease and extent of resection) but was also highly associated with the histologic groupings of medulloblastoma. Histologically, medulloblastoma is divided into 5 classes: classic (CL), desmoplastic/nodular (DN), medulloblastoma with extensive nodularity (MBEN), and large cell and/or anaplastic (LC/A). These studies showed that patients with DN or MBEN histology had a much higher PFS (>80%) with IVT-MTX or HDC-AuSCR than those with CL or LC/A (<30%).[9,21,27]

This histopathologic finding suggested that medulloblastoma in infants and young children was not all the same. Outcome and response to CSI avoidance therapy was predicated on the cellular appearance of the disease, and, inferentially, the biologic makeup of the tumor. For the first time, it became important to incorporate histology into risk stratification schemes, and this gave rise to studies aimed at the different histologic types of the disease.

The St. Jude Children's Research Hospital SJYC07 study in young children, launched in 2007, was designed to assess whether EFS could be improved when therapy was adapted based on biologic and clinical risk.[30] The low-risk group targeted infants with M0, GTR, and DN/MBEN histology. The intermediate-risk group treated infants with M0, GTR, CL, or LC/A histology and young

Table 1. Selected Historical Clinical Trials That Enrolled Infants and Young Children With Medulloblastoma

Study	Treatment	Results		
		Outcome	Pathology	Molecular Features
POG-1[18] 1986–1990 Patients aged <36 mo with newly diagnosed brain tumor (N=62 [MB]) **M+ and M0 at diagnosis**	**Radiation-delaying strategy** Cycle A: CPM + VCR Cycle B: CDDP + VP16 Repeated courses of A and B cycles from diagnosis until age 3 y	• 5-y PFS: 31.8% ± 8.3% (WC-MB) • 5-y OS: 39.7% ± 6.9% (WC-MB) • 5-y PFS: 69% (GTR/M0) • 5-y PFS: 32% (STR [M0/M+])		
HIT-SKK'87[21] 1987–1993 Patients aged <3 y with newly diagnosed brain tumor (N=32 [MB]) **M+ and M0 at diagnosis**	**Radiation-delaying strategy** Procarbazine, MTX, CDDP, Ifos, VP16, ARAC until age 3 y then CSI	• 10-y PFS: 48.3% ± 9.3% (WC-MB) • 10-y OS: 55.2% ± 9.3% (WC-MB) • 10-y PFS: 52.9% ± 12.1% (GTR/M0) • 10-y OS: 58.8% ± 11.9% (GTR/M0) • 10-y PFS: 0.0% (M+) • 10-y OS: 0.0% (M+)	• 10-y PFS: 88.9% ± 10.5% (DN) • 10-y OS: 88.9% ± 10.5% (DN) • 10-y PFS: 30.0% ± 10.3% (CL) • 10-y OS: 40.0% ± 11.0% (CL)	
CCG-9921[20] Activated–1993 Patients aged <36 mo with newly diagnosed brain tumor **M+ and M0 at diagnosis**	**Radiation-delaying/ radiation-sparing strategy** Induction strategy: A: VCR, CPM, CDDP, VP16 B: VCR, Carbo, Ifos, VP16 Maintenance: VCR, VP16, Carbo, CPM CSI: GTR/M0 (at the end of induction): *CSI only after progression* STR/M+: *CSI at age 36 mo* Progression: *CSI regardless of age*	• 5-y PFS: 32% ± 5% (WC-MB) • 5-y OS: 43% ± 5% (WC-MB) • 5-y EFS: 41% ± 8% (GTR/M0) • 5-y OS: 54% ± 8% (GTR/M0) • 5-y EFS: 25% ± 8% (M+) • 5-y OS: 31% ± 9% (M+)		
CCG-99703[26] 1998–2004 Patients aged <36 mo with malignant brain tumor **M+ and M0 at diagnosis**	**Radiation-sparing HDC-AuSCR** Induction: CDDP, CMP, VCR, VP16 Consolidation HDC: Carbo and Thiotepa and AuSCR	• 5-y EFS: 43.9% ± 5.2% (WC) • 5-y OS: 63.6% ± 5% (WC) • 5-y EFS: 54.4% ± 7% (GTR) • 5-y OS: 75.9% ± 8% (GTR) • 5-y EFS: 28.9% ± 7% (<GTR) • 5-y OS: 48.7% ± 8% (<GTR) • 5-y EFS: 67.5% ± 9.5% (M0) • 5-y EFS: 30% ± 14.5% (M+)	• 5-y EFS: 78.6% ± 11% (DN) • 5-y OS: 85.7% ± 9.4% (DN) • 5-y EFS: 50.5% ± 12% (other) • 5-y OS: 60.6% ± 11.6% (other)	
Head Start (HS) I/II[24] 1997–2002 Patients aged <36 mo with newly diagnosed MB **Only M0 reported**	**Radiation-sparing HDC-AuSCR** Induction: CDDP, CPM, VP16, VCR (HS II MTX only if M+) Consolidation: HDC: Thiopeta, VP16, Carbo, and AuSCR	• 5-y EFS: 52% ± 11% (WC/M0) • 5-y OS: 70% ± 10% (WC/M0) • 5-y RFS: 52% ± 11% • 5-y EFS: 64% ± 13% (GTR/M0) • 5-y OS: 79% ± 11% (GTR/M0) • 5-y EFS: 29% ± 17% (STR/M0) • 5-y OS: 57% ± 19% (STR/M0)	• 5-y EFS: 67% ± 16% (DN) • 5-y OS: 78% ± 14% (DN) • 5-y EFS: 42% ± 14% (CL) • 5-y OS: 67% ± 14% (CL)	
Head Start (HS) III[9] 2003–2009 Children aged <10 y with MB **Including M+ and M0**	**Radiation-sparing HDC-AuSCR** Induction: Cycles 1, 3, 5: CDDP, CPM, VP16, VCR Cycles 2, 4: CPM, VCR, VP16 (oral), TMZ (oral) Consolidation: HDC: thiotepa, VP16, Carbo, and AuSCR RT at physician discretion	• 5-y EFS: 46% ± 5% (WC) • 5-y OS: 62% ± 5% (WC) • 5-y EFS: 61% ± 8% (M0) • 5-y OS: 77% ± 7% (M0) • 5-y EFS: 35% ± 7% (M+) • 5-y OS: 52% ± 7% (M+)	• 5-y RFS: 78% ± 8% (DN) • 5-y RFS: 21% ± 5% (CL/LC/A)	
HIT-SKK'92[27] 1992–1997 Patients with newly diagnosed MB, aged <3 y at diagnosis **M+ and M0**	**Radiation-sparing IVT-MTX** Chemotherapy: HD-MTX, IVT-MTX, Carbo, CPM, VP16, and VCR	• 5-y EFS: 52% ± 11% (WC/M0) • 5-y OS: 70% ± 10% (WC/M0) • 5-y EFS: 64% ± 13.0% (GTR/M0) • 5-y OS: 79% ± 11% (GTR/M0) • 5-y EFS: 29% ± 17% (STR/M0) • 5-y OS: 57% ± 19% (STR/M0)	• 5-y EFS: 67% ± 16% (DN) • 5-y OS: 78% ± 14% (DN) • 5-y EFS: 42% ± 14% (CL) • 5-y OS: 67% ± 14% (CL)	
HIT-SKK 2000[28] 2001–2005 Patients aged <3 y with newly diagnosed MB **Only M0**	**Radiation-sparing IVT-MTX** Chemotherapy: HD-MTX, IVT-MTX, Carbo, CPM, VP16, and VCR	• 5-y EFS: 57% ± 8% (WC/M0) • 5-y OS: 80% ± 6% (WC/M0)	• 5-y EFS: 90% ± 10% (DN) • 5-y OS: 100% (DN) • 5-y EFS: 30% ± 11% (CL) • 5-y OS: 68% ± 10% (CL)	

(*continued on next page*)

Table 1. Selected Historical Clinical Trials That Enrolled Infants and Young Children With Medulloblastoma (cont.)

Study	Treatment	Results		
		Outcome	Pathology	Molecular Features
HIT-SKK'2000BIS4[28] 2001–2011 Patients aged <3 y with newly diagnosed MB **Only M0**	**Radiation-sparing IVT-MTX** Chemotherapy: HD-MTX, IVT-MTX, Carbo, CPM, VP16, and VCR LC/A/CL histology received focal RT until 2006	• 5-y PFS: 64% (WC/M0) • 10-y PFS: 64% (WC/M0) • 5-y OS: 80% (WC/M0) • 10-y OS: 72% (WC/M0) • 5-y CSI-free survival: 65% (WC/M0) • 10-y CSI-free survival: 63% (WC/M0)	• 5-y EFS: 93% (DN) • 5-y OS: 100% (DN) • 5-y EFS: 37% (CL) • 5-y OS: 67% (CL)	• 5-y PFS: 93% (SHH) • 5-y OS: 100% (SHH) • 5-y PFS: 73% (SHH-1) • 5-y OS: 88% (SHH-1) • 5-y PFS: 83% (SHH-2) • 5-y OS: 97% (SHH-2) • 5-y PFS: 36% (G3) • 5-y OS: 49% (G3) • 5-y PFS: 85% (G4) • 5-y OS: 100% (G4)
SJYC07[30] 2007–2017 Patients aged <3 y with newly diagnosed MB **M+ and M0**	**Low-intensity chemotherapy (no IVT-MTX or HDC-AuSCR)** Induction: HD-MTX, CDDP, CPM, VCR, Carbo, VP16, Topo Low risk: M0 DN/MBEN patients aged <3 y treated → low-intensity consolidation (chemotherapy) Intermediate risk: M0 CL/LC/A patients aged <3 y and M0 DN/MBEN 3–5 → focal radiation High risk: M+ patients aged <3 y → higher-intensity consolidation (chemotherapy)	• 5-y EFS: 31.3% (WC) • 5-y OS: 59.4% (WC) • 5-y EFS: 55.3% (LR) • 5-y-OS: 85.9% (LR) • 5-y EFS: 24.6% (IR) • 5-y OS: 52.8% (IR) • 5-y EFS: 16.7% (HR) • 5-y OS: 41.0% (HR)	• 5-y EFS: 52.5% (DN) • 5-y OS: 75.3% (DN) • 5-y EFS: 13.8% (CL) • 5-y OS: 49.2% (CL)	• 5-y PFS: 51.1% (SHH) • 5-y OS: 71.9% (SHH) • 5-y PFS: 27.8% (SHH-1) • 5-y PFS: 22.2% (SHH-1 LR) • 5-y OS: 60.6% (SHH-1) • 5-y PFS: 75.4% (SHH-2) • 5-y PFS: 90.9% (SHH-2 LR) • 5-y OS: 83.8% (SHH-2) • 5-y PFS: 8.3% (G3) • 5-y OS: 47.1% (G3) • 5-y PFS: 13.3% (G4) • 5-y OS: 57.1% (G4)
ACNS1221[40] Patients aged <3 y with newly diagnosed MB with DN/MBEN histology **M0**	**Low-intensity chemotherapy (no IVT or HDC-AuSCR)** HD-MTX, Carbo, CPM, VP16, and VCR	• 2-y EFS: 52.2% (WC) • 2-y OS: 92.0% (WC)	• 2-y PFS: 100% (MBEN) • 2-y PFS: 33.3% (DN)	• 2-y PFS: 30.0% (SHH-1) • 2-y PFS: 66.7% (SHH-2)

Abbreviations: ARA-C, cytarabine; Carbo, carboplatin; CDDP, cisplatin; CL, classic histology; CPM, cyclophosphamide; CSI, craniospinal irradiation; DN, desmoplastic/nodular histology; EFS, event-free survival; G, group; GTR, gross total resection; HD-MTX, high-dose methotrexate; HDC-AuSCR, high-dose chemotherapy with autologous stem cell rescue; HR, high risk; Ifos, ifosfamide; IR, intermediate risk; IVT-MTX, intraventricular methotrexate; LC/A, large cell and/or anaplastic histology; LR, low risk; M+, metastatic disease at diagnosis; M0, nonmetastatic disease at diagnosis; MB, medulloblastoma; MBEN, medulloblastoma with extensive nodularity; MTX, methotrexate; OS, overall survival; PFS, progression-free survival; Pred, prednisolone; RFS, radiation-free survival; RT, radiation therapy; SHH, Sonic Hedgehog; STR, subtotal resection; TMZ, temozolomide; Topo, topotecan; VCR, vincristine; VP16, etoposide; WC, whole cohort.

children (age 3–5 years) with M0, GTR, and DN/MBEN histology. The high-risk group included all infants with metastases. Patients in all risk categories received systemic high-dose MTX (HD-MTX)–based induction chemotherapy, followed by varied-intensity consolidation chemotherapy for the low-risk and high-risk patients and focal RT for the intermediate group. With this treatment, patients with DN/MBEN histology had a 5-year PFS of 52.5%, which was disappointingly lower compared with those treated with higher-intensity therapies (HDC-AuSCR and IVT-MTX).[30] However, this finding did reveal that at least half of patients with DN and MBEN pathology could be cured with lower-intensity chemotherapy, thus reducing treatment-associated toxicity for a select group of patients.

These studies made 3 critical discoveries: (1) tumor biology is a significant prognostic factor along with disease burden, (2) DN/MBEN can be cured without radiation and about half of these patients can be cured with a chemotherapy regimen that does not use intensifications such as IVT-MTX or HDC-AuSCR, and (3) medulloblastoma with CL and LC/A is a therapeutic challenge, because a vast majority are not cured by radiation-sparing chemotherapy of any form (Table 1). Many questions and concerns remain, namely: (1) if half the patients with DN/MBEN benefit from lower-intensity therapy, then is there a way to identify this subset and risk stratify accordingly?, and (2) if >70% of the CL and LC/A, and M+ population experience relapse and inevitably receive CSI therapy, then why continue to subject these patients to high-intensity chemotherapy?

Molecular Landscape of Medulloblastoma in Infants and Young Children

Between 2006 and 2012, 4 independent groups of researchers conducted unsupervised analysis of genomic

expression profiles of medulloblastomas. These studies revealed that medulloblastomas split into distinct molecular groups characterized by either WNT signaling, Sonic Hedgehog (SHH) signaling, expression of neuronal differentiation genes, or photoreceptor genes.[35–38] The identification of these groups transformed the understanding of medulloblastoma from a single-entity disease into a collection of diseases that arise from distinct progenitor cells in the hindbrain. Although all result in space-occupying tumors that grow into the cerebellum, these molecularly grouped medulloblastomas were found to be clinically and molecularly distinct. Eventually, the findings were pooled and 4 consensus molecular groups of medulloblastoma emerged: WNT, SHH, group 3 (G3), and group 4 (G4).[39]

Subsequently, molecular analysis was extended to medulloblastomas in infants and young children and 3 transformative findings were identified: (1) the distribution of molecular groups is vastly different from older children and changes with each year of age, making age at diagnosis an unexpected contributor to outcome variability; (2) there is a very strong association between DN/MBEN histology and the SHH group, making the association between histology and prognosis inextricably linked with tumor biology; and (3) within the molecular groups are molecular subgroups that correlate with outcome, and these can inform risk stratification.

To best summarize these findings, we pooled the molecular data of patients aged <6 years from 5 published studies to generate a cohort of 329 patients.[4,30,40–42] Figure 1A shows that in infants, SHH medulloblastoma is the dominant group, constituting >75% of cases. As for the remaining 25%, most are in G3 category (~20%), with only a small fraction (~5%) in the G4 group. Fascinatingly, the younger the patient, the more likely their tumor is SHH, and as age increases, the distribution shifts. Beyond 3 years, the proportion of the SHH group shrinks to approximately 25%, whereas the G3 and G4 distributions grow to approximately 45% and 30%, respectively (Figure 1A). This distribution is in contrast to older children, in which the WNT molecular group forms 10% and G4 becomes the dominant group (~45%).[2] This phenomenon has consequences for clinical trials because a cohort of infants will reflect the SHH group response, whereas inclusion of young children unwittingly adds a significant number of G3 and G4 patients.

The effect of molecular group distribution is even more important when one realizes that DN/MBEN histology is a surrogate marker for the SHH group. As shown in Figure 1B, 100% of DN/MBEN belong to the SHH group, whereas G3 and G4 tumors are either CL or LC/A. Indeed, when survival is evaluated based on molecular group, the same pattern that was seen in histology emerges. For example, in the HIT-SKK'2000BIS4 study, the PFS for SHH versus G3 was identical to DN/MBEN versus CL/LC/A (Table 1).[28]

Finally, and perhaps most importantly, molecular classification has uncovered substructure within the molecular groups. In 2017, Cavalli et al[43] described 4 subgroups within SHH medulloblastoma, originally called SHHα, SHHβ, SHHγ, and SHHδ. Of these, SHHβ and SHHγ were primarily found in infants and young children. When compared with SHHγ, SHHβ tumors were more often metastatic, displayed more chromosomal copy number variations, and were associated with worse survival.[43] Shortly thereafter, 2 additional studies explored DNA methylation arrays in infants and young children and identified 2 subgroups that they called iSHH-I and iSHH-II.[30] Comparison of the studies showed SHHβ corresponded with iSHH-I and SHHγ with iSHH-II, and consensus nomenclature has redefined these as SHH-1 and SHH-2.[30,40,43]

Analogous to the SHH group, subgroup structure has also been identified within G3 and G4. In fact, distinguishing between G3 and G4 has always been difficult, and recent studies suggest the heterogeneity within the entire G3/G4 group is better defined via multiple subgroups.[42] One of the first studies to show this applied *t*-distributed stochastic neighbor embedding (*t*-SNE) to 740 G3/G4 medulloblastoma samples profiled by DNA methylation and found 8 methylation subgroups (I–VIII).[42] Of these, subgroup IV is the most prevalent in infants (~60%), and only small numbers from I, II, III, VII, and VIII make up the remaining 40% (Figure 1C).

In 2021, these subgroups were incorporated into the WHO classification,[44] in which a 2-tier system is described. The first divides medulloblastoma into 3 molecular groups: (1) WNT-activated medulloblastoma, (2) SHH-activated medulloblastoma, and (3) non-WNT/non-SHH medulloblastoma (G3 and G4).[45] The second adds 4 subgroups of SHH and 8 subgroups G3/G4.[44]

Molecular Profiles Drive Clinical Outcome

Retrospective analyses of trials in the context of molecular groups and subgroups have been both insightful and practice-altering (Table 1). Regarding the groups, as previously mentioned, SHH medulloblastoma mirrors the DN/MBEN outcomes, with PFS without CSI ranging from 50% for low-intensity regimens to 90% for patients with M0, GTR disease receiving IVT-MTX.[28,30] Regarding the subgroups, in SJYC07, a significantly higher PFS was seen in the SHH-2 group compared with the SHH-1 group regardless of metastatic status (75.4% vs 25.8%). Furthermore, when limited to low-risk patients, the difference was even greater (90.9% vs 22.2%).[30] Likewise, in ACNS1221, a similar but less pronounced survival difference was observed.[40] In HIT-SKK'2000BIS4, where patients aged <4 years with M0, GTR medulloblastoma were treated with systemic chemotherapy augmented with IVT-MTX, the 5-year PFS of those in the SHH-1 group was 73% compared with 83% for those

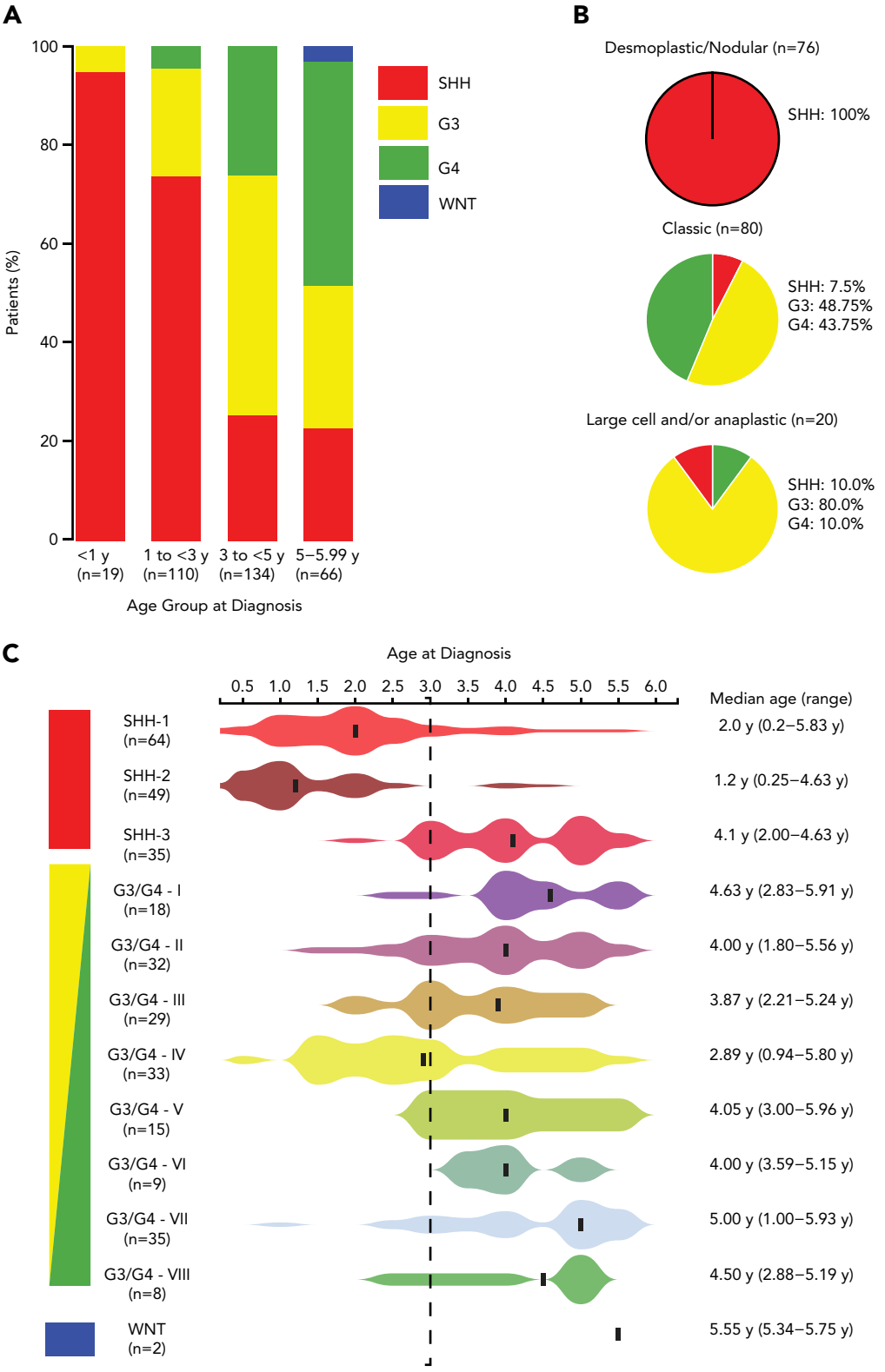

Figure 1. Distribution of molecular groups and subgroups of medulloblastoma in infants and young children by age and histology. Results generated from a combined dataset of published cases of medulloblastoma in infants and young children.[30,40–42] **(A)** Bar graphs show the prevalence of SHH, G3, G4, and WNT molecular groups by age at diagnosis (n=329). **(B)** Pie charts show the distribution of histologic subtypes of medulloblastoma. **(C)** Violin plots depict the prevalence of molecular subgroups by age at diagnosis. The black vertical bar represents median age within the given subgroup.
Abbreviations: G3, group 3; G4, group 4; SHH, Sonic Hedgehog.

in the SHH-2 group.[28] Taken together these studies showed that patients in the SHH-2 group have low relapse rates with low-intensity regimens, whereas the addition of IVT-MTX to systemic chemotherapy provides a substantial benefit to patients in the SHH-1 group, but the outcome of those in the SHH-2 group did not significantly differ. In stark contrast to the beneficial responses seen in SHH, studies consistently show that patients with G3 medulloblastoma are not cured by chemotherapy alone. The 5-year PFS for G3 from SJYC07 was <10% and 36% from HIT-SKK'2000BIS4, which only enrolled those with M0, GTR.[28,30] Even when chemotherapy was given at myeloablative doses (ie, HDC-AuSCR) the survival of patients with G3 medulloblastoma was poor, as demonstrated by a 0% PFS in a small series by Yeo et al.[46]

Although other studies have reported better G3 outcomes, these results are complicated by trial allotments for discretionary radiation given before or after relapse. For example, the PBTC026 trial, which reported a 42% 5-year PFS and 58% 5-year OS in 12 patients with G3 medulloblastoma, treated patients with HDC-AuSCR and focal radiation, and allowed for craniospinal radiation in patients with M+ disease to be given at the discretion of the treating physician.[47] Similarly, ACNS0334, which treated patients with HDC-AuSCR ± HD-MTX, also allowed for discretionary RT and reported in an abstract a 5-year OS of 80% in 10 patients with G3 medulloblastoma treated with HD-MTX and 40% in 15 patients treated without HD-MTX.[48,49] Although this preliminary result with HD-MTX is intriguing, it remains important to tease out the radiation-free and CSI-free survival, especially when one considers the post-relapse survival (PRS) experience.[50]

Studies that include PRS show that patients treated with radiation-sparing regimens receive salvage CSI, and this explains why the OS is higher than the PFS/EFS on the trials (Table 1). In SJYC07, patients with G3 medulloblastoma had a 5-year OS of 49.7% after receiving salvage CSI compared with 18.8% with other salvage modalities. Most recently, Erker et al[50] published the results of >300 infants and young children with relapsed medulloblastoma after radiation-sparing therapy and found salvage regimens with CSI were associated with a 3-year PRS of 60.8% compared with 39.5% without. Moreover, subgroup IV (the most common G3/G4 subgroup in infants) showed excellent PFS (5-year PFS, >85%) when treated with surgery, risk-adapted CSI, and chemotherapy in children aged >3 years, and the SJYC07 relapse data showed good postprogression survival (5-year OS, 62%) despite universal progression.[4,30] Although these numbers are small, these data suggest high cure rates in subgroup IV and better cure rates in G3 are possible if risk-adapted CSI is offered when the child turns 3 years old.

Molecular Classification Paves Way for the Next Generation of Clinical Trials

Although there was hope that the molecular interrogation of medulloblastoma would uncover more targeted therapies with fewer long-term toxicities and remove CSI completely from the treatment paradigm in infants and young children, this has not materialized. Nevertheless, with integrated DNA methylation assigning molecular groups and subgroups, a real opportunity to tailor therapy has emerged that could maximize survival and minimize toxicity within the confines of current therapeutic modalities.

One such strategy emerging from a joint European-North American collaboration (through SIOP and CONNECT consortia) is a clinical trial for patients with only SHH medulloblastoma designed to prospectively compare the IVT-MTX approach to HDC-AuSCR used across the HIT-SKK protocol.

Alternatively, our group at St. Jude has launched a multisite clinical trial (SJiMB21; ClinicalTrials.gov identifier: NCT05535166; Figure 2) to treat all types of infant medulloblastoma. In this trial, age at diagnosis for eligibility is deliberately limited to infants (age <3 years), except for young children (age <5 years) with nonmetastatic SHH-2 medulloblastoma. Patients with SHH-2 disease are assigned reduced-intensity chemotherapy, whereas those with SHH-1 receive therapy intensified by IVT-MTX. Even infants with SHH medulloblastoma with M+ disease at diagnosis will be eligible for this therapy, due to the fact that no significant differences were observed for M+ disease within these subgroups.[30] Those with G3/G4 medulloblastoma, on the other hand, are candidates for pre-relapse risk-adapted proton-beam CSI upon reaching 3 years of age, with patients with M+ disease at diagnosis being stratified into average or high-dose CSI depending on response to chemotherapy. Furthermore, comprehensive supportive care is integrated into the therapy and follow-up (eg, early neurocognitive screening and intervention; early hearing screening for therapy-associated sensorineural hearing loss; and rigorous occupational, physical, and speech therapy). Such a trial aims to not only maximize survival but also attenuate the long-term toxicities of treatment.

Yet, despite these current best efforts, there remains a fraction of young patients who are incurable by current modalities. These patients will predictably have tumors that belong to G3/G4 subgroups II and III and harbor high-risk features like *MYC* amplification and metastasis or who have SHH tumors that contain *TP53* mutations or *MYCN* amplifications.[30] These patients will remain difficult to manage because they often show rapid early progression on chemotherapy and, even with CSI, are not expected to survive in meaningful numbers, making them ideal candidates for novel future therapeutic strategies.

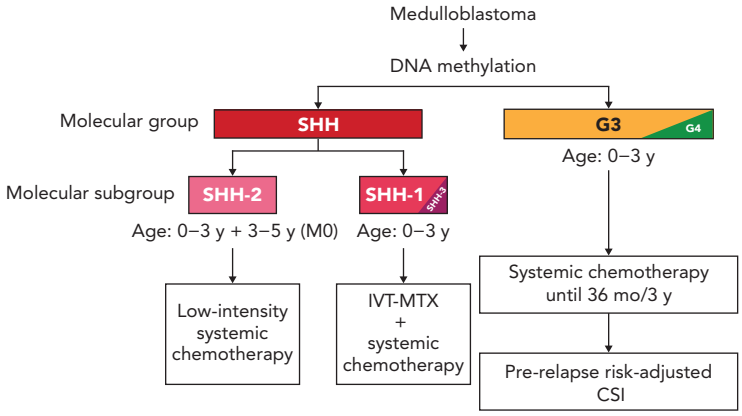

Figure 2. Schematic of SJiMB21, a phase II study of molecular and clinical risk-directed therapy for infants and young children with newly diagnosed medulloblastoma. On this trial, newly diagnosed medulloblastoma in infants and young children up to 5 years of age are evaluated using DNA methylation classification. First, potential patients are divided by molecular group into SHH and G3/G4 tumors. Second, SHH tumors are split into SHH-1, SHH-2, or SHH-3. Infants (age <3 years) with SHH-2 tumors and young children (age 3–5 years) with nonmetastatic (M0) disease are eligible for low-intensity systemic chemotherapy. Infants with SHH-1 tumors are eligible for systemic chemotherapy augmented with IVT-MTX. Infants with G3 or G4 tumors are eligible for systemic chemotherapy until age 3 years and then prescribed pre-relapse risk-based CSI.
Abbreviations: CSI, craniospinal irradiation; G3, group 3; G4, group 4; IVT-MTX, intraventricular methotrexate; M0, non-metastatic disease at diagnosis; SHH, Sonic Hedgehog.

Given that the early molecular studies on medulloblastoma have uncovered so much about this complex and heterogeneous disease, it is exciting to think about what is yet to come. Already, germline predisposition mutations, including *PTCH1*, *SUFU*, *GPR161*, *BRCA2*, *PALB2*, *ELP1*, and *TP53*, caution against excessive carcinogenic exposure and very much support a risk-adapted trial design that can minimize exposure wherever possible.[41,51] Moreover, our increasing ability to detect measurable residual disease through serial measurement of cell-free DNA in the cerebrospinal fluid will improve our understanding of treatment response, and thus carries the potential to optimize the intensity of cancer-directed therapy in real time.[52,53]

Conclusions

Medulloblastoma in infants and young children is a challenge to treat; however, molecular advancements have uncovered a new way forward. By incorporating molecular risk into treatment stratification, we envisage that cure rates will increase and the long-term treatment-related morbidities that have plagued this vulnerable population will decrease.

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