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How I Treat Medulloblastoma in Children

Abstract

Medulloblastoma (MB) is the most common malignant tumor of the central nervous system in children with up to a third of these tumors presenting in children under 3 years of age. Its exquisite radio and chemosensitivity renders high cure rates in children in whom optimal resection has been achieved. Optimal surgery followed by radiation alone can cure about half of these children. The addition of chemotherapy has improved the outcomes dramatically and over 70% of children over 3 years of age with optimal resection and no metastasis can expect to be cured. Increasingly, the focus is on limiting the long-term sequelae of treatment. Precise molecular characterization can enable us to identify patients who can achieve optimal outcomes even in the absence of radiation. Insights into disease biology and molecular characterization have led to dramatic changes in our understanding, risk stratification, prognostication, and treatment approach in these children. In India, there is limited access to molecular profiling, making it challenging to apply biology driven approach to treatment in each child with MB. The Indian Society of Neuro-Oncology guidelines and the SIOP PODC adapted treatment recommendations for standard-risk MB based on the current evidence and logistic realities of low-middle income countries are a useful adjunct to guide clinical practice on a day-to-day basis in our setting.

Keywords: *Childhood, craniospinal irradiation, medulloblastoma, molecular characterization*

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Introduction

Medulloblastoma (MB) is the most common embryonal tumour in children. The mean age at presentation is 9 years, though up to a third of these tumors present in children under 3 years of age. The predominant symptoms are secondary to obstructive hydrocephalus. Patients may also present with ataxia, cranial neuropathies or nerve root/spinal cord compression. The symptoms may be gradually progressive over weeks to months. 10%–40% of patients have central nervous system dissemination at diagnosis, with infants having the highest incidence. Imaging of the entire craniospinal axis is, therefore, vital at initial evaluation.

There have been major strides in the understanding of the biology and molecular characterisation of MB which are now being used to personalize management. Conventionally, MB has been classified based on histology (classic, desmoplastic/nodular [DNMB], MB with extensive nodularity [MBEN], large cell/anaplastic). Besides, MB is currently classified into four distinct molecular subgroups according to transcriptional profiling studies[1] - WNT, sonic hedgehog (SHH), Group 3, and Group 4 with prognostic implications. The molecular profiling correlates both with clinical outcomes and histologic appearance. The World Health Organization 2016 guidelines classify MB based on histology and genetically.[2,3] Table 1 depicts the current classification.

The Indian Society of Neuro-Oncology guidelines and the SIOP-PODC guidelines for MB provide a pragmatic approach to the management of this condition in our setting.[4,5]

Case 1

Standard risk medulloblastoma in >3 years old

A 5-year-old boy presented with headaches and clumsiness starting 3 months prior to presentation. Headaches were worse in the morning and relieved by vomiting. Ophthalmic review revealed papilledema and nystagmus. His development had been normal prior to these symptoms.

Physical examination revealed ataxic gait. Urgent neuroimaging with magnetic

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resonance imaging (MRI) [Figure 1] revealed a mass lesion in the region of the 4th ventricle with hydrocephalus. Screening MRI of the spine revealed no evidence of leptomeningeal disease. He underwent midline suboccipital craniotomy, external ventricular drainage (EVD), and tumor resection. Histopathology confirmed classical MB with subsequent IHC-based assignation into the non-WNT, non-SHH subgroup.

Postoperative imaging [Figure 2] did not demonstrate any hemorrhage and confirmed near-total resection (NTR).

Three weeks postoperatively, lumbar puncture was done for cytopathological evaluation and was negative for malignant cells. The patient was commenced on adjuvant radiation 54 Gy with 23.4 Gy to the craniospinal axis. Radiotherapy could be completed without undue interruptions and delay.

Reassessment MRI performed 4 weeks after completion of radiation revealed no evidence of residual disease. Baseline neurological, endocrine, and auditory evaluations were performed. Adjuvant chemotherapy was commenced with vincristine, cyclophosphamide, and cisplatin. A total of six cycles were delivered. The patient continues on surveillance with MRI brain every 3 months in the 1st year and screening MRI of the spine every 6 months. Growth, development, and neurocognitive functioning is assessed every 6 months.

Optimal management of MB in the current era mandates precise risk stratification incorporating stage, postsurgical status, histology, and molecular characterization.

Diagnosis and staging

The diagnosis is established with a contrast-enhanced MRI. Ideally, the entire neuraxis should be evaluated prior to surgery. Postoperative imaging may be confounded by artifacts especially blood. All patients must undergo cerebrospinal fluid (CSF) analysis 2–3 weeks after surgery. Up to 10% of patients may have malignant cells in CSF in the absence of radiological evidence of leptomeningeal dissemination. CSF analysis done earlier than 2 weeks post-operatively may be misleading. Bone marrow examination or bone scans are not routinely indicated at diagnosis unless patients are symptomatic.

The tumor extent is defined based on the presence and extent of neural and extraneural metastasis [Table 2]. The extent of resection is the most significant factor affecting prognosis. This is defined on the basis of postoperative residual disease [Table 3]. Recent evidence,[6] however, indicates that the prognostic benefit of increased extent of resection depends on the molecular subgrouping. Maximal safe surgical resection continues to be the standard of care but repeat surgery to resect small residual portions of MB is not recommended if the likelihood of neurological morbidity is high. There is no definitive benefit to gross total resection compared with NTR. Specifically for patients with WNT, SHH, or Group 3 tumors, there is no significant survival benefit with gross total resection versus subtotal resection. For Group 4 tumors, gross total resection confers better progression-free survival.

Table 1: Classification of medulloblastoma

Medulloblastoma genetically defined
Medulloblastoma, WNT-activated
Medulloblastoma, SHH-activated and *TP53*-mutant
Medulloblastoma, SHH-activated and *TP53*-wild-type
Medulloblastoma, non-WNT/non-SHH
Medulloblastoma, Group 3
Medulloblastoma, Group 4
Medulloblastoma, histologically defined
Medulloblastoma, classic
Medulloblastoma, desmoplastic/nodular
MBEN
Medulloblastoma, large cell/anaplastic
Medulloblastoma, NOS

NOS: Not otherwise specified, MBEN: Medulloblastoma with extensive nodularity, SHH: Sonic hedgehog

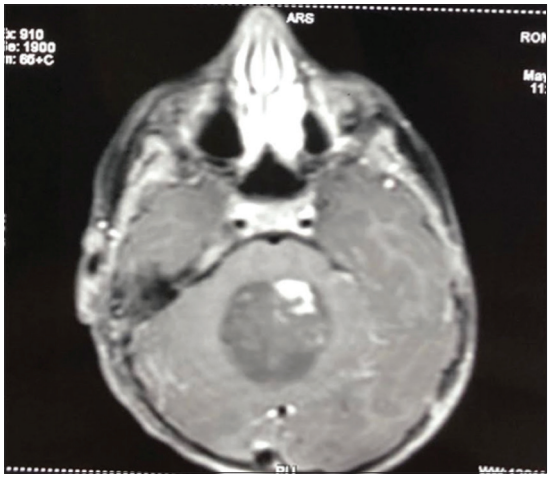

Figure 1: Standard risk medulloblastoma in >3 years old

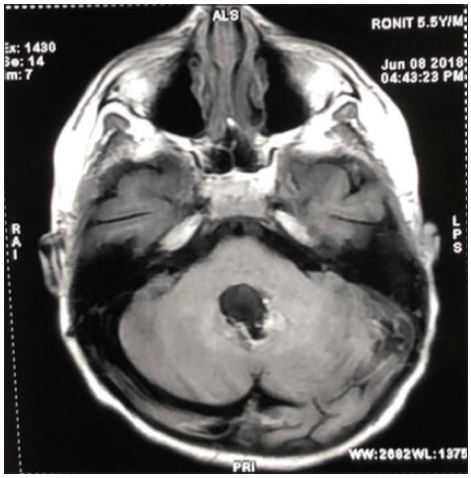

Figure 2: Standard risk medulloblastoma-postoperative

Table 2: Staging of medulloblastoma

M_0: No dissemination
M_1: CSF-positive cytology only
M_2: Gross nodular seeding in cerebellar-cerebral subarachnoid space and/or lateral or third ventricle
M_3: Gross nodular seeding in spinal subarachnoid space
M_4: Extraneural metastasis

CSF: Cerebrospinal fluid

Table 3: Classification based on postoperative residual disease

GTR: No radiographical evidence of disease
NTR: ≤1.5 cm^2 residual disease after resection
STR: >1.5 cm^2 of measurable residual disease
Biopsy: No tumor resection; only a sample of tumor tissue removed

STR: Subtotal resection, GTR: Gross-total resection, NTR: Near-total resection

Genetics

Genomic profiling currently identifies four distinct subgroups WNT, SHH, Group 3, and Group 4. These molecular subtypes may further be classified based on the presence of MYC or MYCN alterations, TP53, and other genomic alterations.[7,8]

The WNT and SHH classifications define the oncopathogenic pathway, while Groups 3 and 4 retain generic designations. WNT tumors are a result of unregulated WNT signalling leading to increased transcriptional activity and tumorigenesis. WNT MB lacking somatic CTNNB1 mutation should ideally be tested for germline APC mutations (familial adenomatous polyposis syndrome) as they have significantly lower long-term survival due to deaths from second tumors, which may potentially be improved with diagnosis and surveillance.[9]

Oncogenesis in SHH MBs results from up regulation of SHH signaling as a direct consequence of loss of function of the tumor suppressor of fused gene (SUFU) and patched-1 (PTCH1). Young children with SHH MB should be screened for germline PTCH1 and SUFU and older children with TP53 mutations for Li-Fraumeni syndrome.[9]

Children with MB with WNT pathway activation have an excellent prognosis.[10] The prognosis of patients with SHH pathway-activated tumors is influenced by the presence or absence of *TP53* mutations.[11] The outcome for the remaining patients is inferior to that for patients with WNT pathway activation.

WNT, SHH, Group 3, and Group 4 MBs account for 10%, 30%, 25%, and 35%, respectively. WNT tumors are usually seen in children and adults, Group 3 tumors are more often seen in infants and children whilst SHH and Group 4 lesions are seen across all age groups. The SHH tumors exhibit a bimodal age distribution, typically occurring in patients <4 and >16 years of age. The biological behavior of SHH MB depends on the age at diagnosis with implications both on management and prognosis.[12]

While having immense prognostic and therapeutic implications, molecular profiling using genome-wide expression profiling studies is not routinely available to the vast majority of patients in low-middle income countries (LMIC). However, in experienced hands, immunohistochemistry based studies can classify the tumors into WNT, SHH, and non-WNT/non-SHH subgroups. Although it is not possible to differentiate between Groups 3 and 4 using this approach, it still offers a pragmatic approach to classify these tumours with therapeutic and prognostic implications.[13]

The role of radiogenomics in the evaluation of MB is evolving and may especially be valuable in LMIC settings. For example, cerebellar hemispheric tumor is likely to be SHH and a midline tumor without significant enhancement is likely to be subgroup 4 MB.[14,15] In addition, many centers in LMIC do have access to FISH studies for MYC, MYCN, and Sanger seqencing for TP53. These, together with IHC and radiology, may help in risk stratification.

Histologic correlation

Although not absolute, there is a correlation between the molecular subgroup and histologic type, for example, 97% of WNT MBs are of the classic histologic variant. In infants, children, and adults, 89%, 25%, and 100% of DNMBs were of the SHH molecular subgroup, respectively. LC/A tumors in infants are usually Group 3 lesions, but are evenly distributed across molecular subgroups in other ages.[16]

Risk stratification

Risk assignation for children older than 3 years of age into average and high-risk prognostic groups is based on the presence of metastatic disease and residual tumor postresection of less or greater than 1.5 cm^2. Patients having postoperative residual tumor >1.5 cm^2, evidence of radiographic metastases, or presence of leptomeningeal disease/CSF seeding are classified as "High-risk," with the remaining patients defined as "average-risk."[2] Children less than 3 years of age constitute a unique group in which current standard of care is chemotherapy alone as a first-line adjunct therapy, with radiation therapy (RT) omitted to avoid the very poor neurocognitive outcomes associated with craniospinal irradiation (CSI) in very young patients.

Given the poor outcomes in patients with diffuse anaplasia,[17,18] it is also recommended that patients with LC/A histology be classified as high risk, irrespective of other adverse features. The current consensus guidelines[2] suggest integrating molecular subgrouping, clinical and radiological features into low risk, standard risk, high risk, and very high-risk categories with distinct survival outcomes [Table 4].

Table 4: Consensus risk-stratification for medulloblastoma in the molecular era

Risk category	WNT	SHH	Group 3	Group 4	Others
Low risk (Expected survival >90%)	< 16 years				
Standard risk (Expected survival 75-90%)		TP53 wildtype No myc amplification No metastasis	No myc amplification and Non-metastatic	Non-metastatic with Chromosome 11 loss	
High risk (Expected survival 50-75%)		One or both: Myc amplification Metastatic		Non-metastatic without Chromosome 11 loss	
Very high risk (Expected survival <%)	Metastatic	TP53 mutation (Metastatic or non-metastatic)	Metastatic	Metastatic	
Unknown			Non-metastatic with MYC amplification; anaplasia; isochromosome 17q	Anaplasia	Melanotic medulloblastoma Medullomyoblastoma Indeterminate between group 3 and 4

Case 2

High-risk medulloblastoma in >3 years old

An 8-year-old boy presented with headache, vomiting, ataxia, and head tilt for 2 weeks. Neuroimaging revealed a well circumscribed lesion 4 cm × 4 cm × 3.8 cm in the region of vermis [Figure 3].

The patient was taken up for surgery. He underwent suboccipital craniotomy with transvermian approach splitting the inferior aspect of the vermis. The tumor was highly vascular and noted to be involving the floor of the fourth ventricle, bilateral foramina of Luschka, and left cerebellar peduncle. Immediate postoperative imaging was not feasible. The patient underwent repeat MRI, 3 weeks postoperatively which revealed residual tumor of 2.5 cc. MRI of the spine demonstrated two focal enhancing nodules in the cervical and thoracic spine. CSF was positive for malignant cells. Molecular profiling confirmed it to be Group 3 MB with myc-amplification.

He received CSI 35 Gy in 21 fractions with posterior fossa boost of 19.8 Gy with concurrent daily carboplatin. He was commenced on chemotherapy 4 weeks' following completion of radiation with vincristine/cisplatin/CCNU and cyclophosphamide. Figure 4 MRI post radiation in child with STR.

Surgical management

Optimal surgery is the cornerstone of management. The extent of resection largely depends on the anatomy of the tumor determining what can be done safely without incurring significant neurological deficit. Many studies support a relationship of extent of resection with progression-free survival. A retrospective analysis of 233 children in a randomized controlled trial of differing

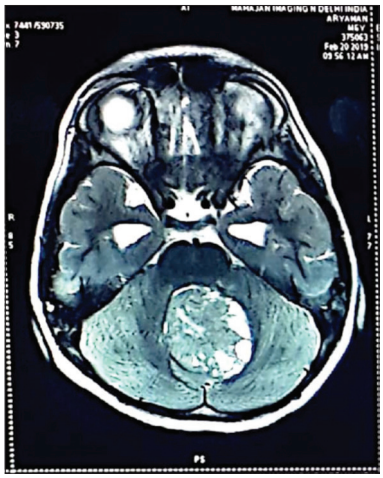

Figure 3: High risk medulloblastoma-preoperative

chemotherapy regimens indicated that residual tumor less than 1.5 cm^2 was associated with improvement in 5-year progression free survival (PFS) of >20% in patients with M0 disease and an 11% difference for all patients irrespective of all other factors.[19] Subsequent studies have questioned this premise when taking into account biological factors. A recent retrospective analysis of 787 patients demonstrated that the benefit of extent of resection is largely attenuated after taking into account molecular subtype and not significant when comparing STR (>1.5 cm^2) versus NTR (<1.5 cm^2) or GTR versus NTR. For tumors involving the brainstem, investigators found no difference in outcome between GTR and residual tumor <1.5 cm^2[6] Aggressive resection of brainstem disease with potential of high morbidity is, therefore, not warranted in view of the sensitivity of the tumor to radiation and chemotherapy.

Children typically present with features of raised ICP due to obstructive hydrocephalus. However, routine preoperative ventriculoperitoneal shunt should be avoided as definitive surgical resection readily relieves the obstruction. Ventricular diversion if needed may be achieved by EVD or an endoscopic third ventriculostomy[20,21] taking care to avoid rapid decompression of the ventricles and overdrainage. Corticosteroids may be required in the preoperative period. Dexamethasone in a loading dose of 0.5–1 mg/kg intravenously (maximum dose 10 mg) followed by 0.25–0.5 mg/kg/day can be given in divided doses.

It is imperative that wherever feasible, screening of the spine should be is done prior to surgery. If not feasible preoperatively, it should be acquired postoperatively 2–3 weeks after surgery to reduce the chance of erroneous interpretation consequent to postoperative enhancement of spinal leptomeninges.[22]

All patients must undergo lumbar puncture and CSF cytopathology to evaluate for dissemination 2–3 weeks' following surgery. Intraoperative samples taken from ventricles do not suffice for this purpose.[23]

The postoperative clinical course can be complicated by the posterior fossa syndrome or cerebellar mutism syndrome in 8%–24% of infratentorial tumor resections. It usually presents in the first 2 days following surgery and is characterized by a triad of cerebellar mutism, ataxia/axial hypotonia, and irritability and emotional lability. These children are commonly apathetic, and/or hypokinetic. While pathophysiology is poorly understood, possible mechanisms include disruption of the dentate-thalamo-cortical pathway, vermian injury, postoperative vasospasm, axonal injury, and neuronal dysfunction.[24,25]

Radiation

Postoperative adjuvant RT is an integral component of therapy for all children above 3 years of age. In view of the high propensity of the tumor to develop leptomeningeal disease, CSI followed by boost irradiation of the tumor bed/posterior fossa is recommended to achieve adequate disease control preferably delivered from a linear accelerator.

The recommended dose is 54–55 Gy delivered over 6–6.5 weeks using conventional fractionation. The dose for CSI for rigorously staged standard risk MBs is 23.4 Gy in 13 fractions followed by tumor-bed boost (30.6 Gy in 17 fractions) to a total tumor-bed dose of 54 Gy in 30 fractions over 6 weeks. Such therapy in conjunction with adjuvant multiagent systemic chemotherapy results in excellent long-term survival outcomes[26,27] but with reduced neurocognitive and endocrinological sequelae compared to the higher doses of CSI. High risk disease is treated with full-dose CSI (35–36 Gy in 20–21 fractions) plus posterior fossa boost (18–19.8 Gy in 10–11 fractions) to a total tumor dose of 54–55 Gy in 30–32 fractions over 6–6.5 weeks. Patients with diffuse leptomeningeal dissemination should receive extended dose CSI (39.6–40 Gy in 22–24 fractions) plus entire posterior fossa boost (14.4 Gy in 8 fractions). A boost of 5.4–9 Gy in 3–5 fractions to focal nodular metastatic deposits in the brain and/or spine can be delivered concurrently during posterior fossa boost irradiation.

Adjuvant RT should ideally begin within 4 weeks of surgery, but definitely within 6 weeks post surgery. Routine use of steroids and GCSF is avoided but may be required.

Proton therapy, where available, may be preferred over photons primarily to limit the burden of both short and long-term effects attributable to radiation.[28,29] However, lack of access to this modality limits it to a very small minority of patients in our setting.

Conventionally, radiosensitizing chemotherapy with concurrent weekly vincristine has been used extensively and is tolerated well in young children. However, there is limited evidence of its role and in view of the significant morbidity attributable to neuropathy especially in older children and adolescents, a number of current protocols omit weekly vincristine in this cohort.

For "high risk" lesions addition of daily carboplatin to weekly vincristine has been evaluated.[30] Carboplatin is potent radiosensitizer and this approach appears to enhance outcomes for this patients with metastatic disease. However, it is important to remember that delivering uninterrupted RT is more important than adding Carboplatin as a radiosensitizer. The ACNS0332 Phase III data suggest no benefit in response or survival with this strategy.

It is ideal to document neurocognitive, endocrinal, and auditory status prior to initiation of adjuvant therapy to establish a baseline for future comparisons.

Chemotherapy

Adjuvant chemotherapy, in the current era is an integral part of the management of MB in children.[26,31] For children above 3 years, adjuvant chemotherapy should ideally start within 4 weeks of radiation, but definitely within 6 weeks. This period is required for hematological recovery. Neuraxial imaging should be done for re-assessment of the disease status prior to the initiation of adjuvant chemotherapy. A total of 6–8 cycles of adjuvant chemotherapy should be administered generally cycled at 3–6 weekly intervals depending on the regimen used. A number of regimens may contain platinum and it is therefore prudent to monitor with audiometry during the treatment as well. The risk of ototoxicity is higher if cisplatin dose in individual cycle exceeds 100 mg/m^2 or cumulative doses exceed 300 mg/m^2.[32] The current evidence indicates that it may not be necessary to deliver cumulative Cisplatin doses of upto 600 mg/m^2 scheduled in older protocols. Lower doses may be equally effective.[33] Attempt should be made to deliver optimal

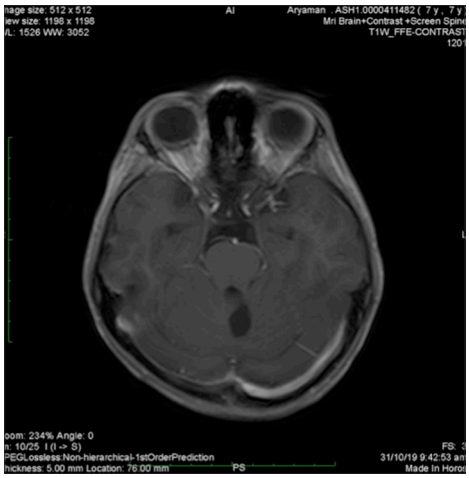

Figure 4: High risk medulloblastoma-postradiation

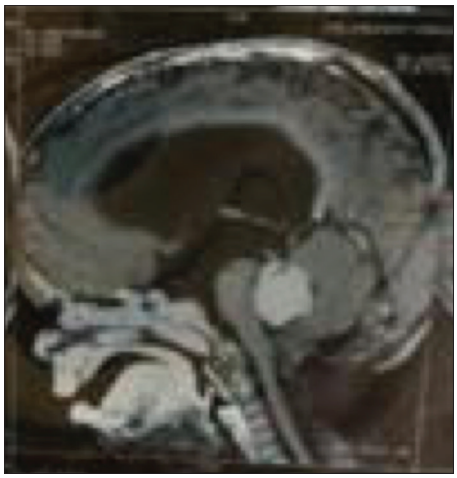

Figure 5: Meulloblastoma in <3 years old

cumulative doses of cyclophosphamide (12 g/m^2) and Cisplatin (300–400 mg/m^2).[31] For children under 3 years of age, adjuvant therapy comprises of primarily chemotherapy with delayed or no radiation to spare young children from devastating late effects.[34-38]

High-dose chemotherapy with stem cell rescue has been evaluated for MB. It is feasible, and may offer an advantage in patients with metastatic or recurrent disease. It offers no survival advantage in older children receiving CSI and in LMIC may be reserved for patients with recurrent disease only. Prior CSI may render stem cell mobilization difficult but plerixafor can overcome this.[39-41]

The Milan strategy for metastatic MB incorporated intensive chemotherapy with myeloablative chemotherapy in selected cases along with hyperfractionated radiation yielded excellent outcomes. However, similar results could not be achieved by other centres with this strategy and it is no longer being actively pursued.[42]

Case 3

Medulloblastoma in <3 years old

A 21-month-old child presented with irritability, and increasing head size for 3 months. Neuroimaging revealed a large 4th ventricular tumor with marked hydrocephlus [Figure 5]. He underwent midline suboccipital craniotomy with microsurgical gross total excision of the tumor with duraplasty [Figure 6]. The right frontal 3rd ventriculostomy was done prior to tumour excision. Histology confirmed MB of the desmoplastic nodular type. Molecular studies confirmed SHH activated variant. Postoperative imaging revealed no residual disease.

The patient was commenced on systemic chemotherapy as per HIT SKK regimen with 12 cycles comprising of carboplatin, methotrexate, cyclophosphamide, and etoposide. Ommaya reservoir was inserted to deliver ventricular methotrexate in each cycle to a total of 32 doses.[35]

The patient was reassessed after every 4 cycles to confirm continuing remission. Decision was taken to omit radiation altogether. The patient continues to be free of disease 2 years' post completion of therapy.

Up to one-third of cases of MB occur during the first 3 years of life. Historically, the survival rates for this cohort have been poor and did not exceed 25%–45% until the past decade. The relatively unfavorable prognosis may partly be explained by more frequent occurrence of metastases and the different biology of MB in young children. Further, the immature brain is particularly susceptible to radiotherapy-induced neurocognitive deficits warranting the omission of this modality.

Treatment strategies for young children with MB have been aimed at improving survival whilst limiting neurocognitive sequelae. Treatment approaches have been focused on delaying or omitting radiotherapy using conventional systemic chemotherapy incorporating high dose and intra-ventricular methotrexate, high-dose chemotherapy with autologous stem cell rescue and tandem transplant following induction chemotherapy with/without high dose methotrexate.[34-38]

The pilot trial HIT-SKK'87 confirmed that postoperative chemotherapy may successfully delay the start of radiotherapy.[34] Intraventricular methotrexate was introduced as a substitute for radiotherapy in the subsequent HIT-SKK'92 trial and HIT 2000 study.[35] If complete remission was achieved, survival rates, especially for young patients with DMB (5-year PFS and OS 85% and 95% respectively were very favorable. Neurocognitive deficits were reduced as compared with the HIT-SKK'87 trial. The estimated survival rates for the entire cohort (5-year EFS rate, 57% + 8%; 5-year OS rate, 80% + 6%) compared favorably with results of older studies.

Exclusively chemotherapy-based approach as first-line treatment may contribute to improved salvage strategies at relapse: while 50% relapses were successfully salvaged in

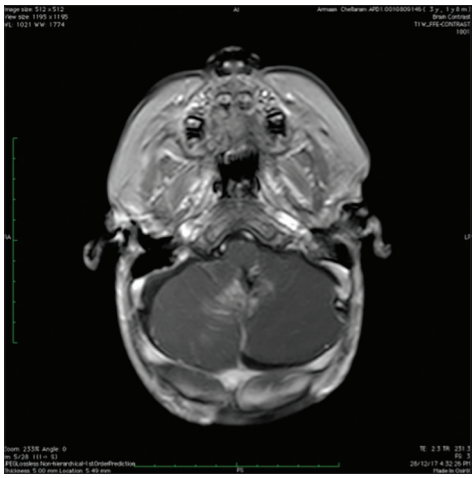

Figure 6: Medulloblastoma in <3 years old-postoperative

HIT-SKK' 92, only 1 of 10 treated children were salvaged in HIT-SKK' 87 trial.

These studies also confirmed that histology is a strong prognostic factor in this age group. This is important as DMB/MBEN account for 40% of cases in this cohort.[38] Gross total resection appears to be more common and feasible for patients with DMB or MBEN. All infants with SHH MB have a favorable prognosis regardless of histology.

For children with non-DMB/non-MBEN, for which predominantly local relapses lead to less favorable survival rates, local radio-therapy has been introduced after chemotherapy since 2006. However, infants with non-SHH MB mainly belong to Subgroup 3 and usually succumb to metastatic disease, and focal RT approaches have failed to improve outcomes in this cohort. The best results till date are with the COG0334 protocol on the high-dose methotrexate arm added to the 99,703 tandem transplant backbone (to be published). Therefore, careful consideration is needed prior to offering focal RT to infant with subgroup 3 MB as this may not have any survival benefit.

The SJYC07 Phase II[43] study offered molecularly driven risk adapted therapy for young children with MB. The study identified a good responder SHH subtype (iSHH-II) that exhibits excellent progression-free survival in the absence of radiation, intra-ventricular or high-dose chemotherapy in contrast to the poor responder iSHH-I that has much inferior outcomes.

Recent data incorporating genomics now mandates that future approaches for young children will increasingly incorporate molecularly driven, risk-adapted approaches.

Follow-up after treatment

Surveillance imaging during and after treatment aimed at detecting recurrent disease at an early stage in asymptomatic patients, has been arbitrarily determined and not been shown to influence survival. Isolated spinal recurrences are infrequent and follow-up imaging must be tailored based on risk assignment.[44] It is imperative that strategies for follow-up incorporate multidisciplinary review inclusive of audiological, neuropsychological and endocrine evaluations.

Case 4

Recurrent medulloblastoma

A 7-year-old young girl had been diagnosed with classical MB at 5 years of age. She had undergone gross total resection and received adjuvant radiotherapy and chemotherapy. One year after completion of chemotherapy, she presented with recurrent disease locally. Surgical resection was attempted followed by high-dose chemotherapy with stem cell rescue. Unfortunately, despite this the disease progressed and she succumbed.

Options for recurrent disease are currently limited and largely unsuccessful. The pattern of failure is likely subgroup-specific and can guide management decisions. Eg: Group 3 and Group 4 usually have distant recurrence after RT-based treatment. SHH-MB may recur both locally and with distant metastasis. Patients with germline conditions are also at risk of second malignancies which need to be recognized and appropriately managed.

Surgery, re-irradiation, and chemotherapy regimens including myeloablative chemotherapy have been explored with poor results.[45,46] A proportion of infants treated previously with only chemotherapy may be salvaged with CSI with profound neurocognitive sequelae. Bevacizumab and irinotecan with or without temozolomide has been shown to give objective response rate and is well tolerated.[47]

An evolving alternative approach is to target tumor angiogenesis with metronomic therapy incorporating bevacizumab, thalidomide, celecoxib, fenofibrate, etoposide, and cyclophosphamide and additional intraventricular therapy (etoposide and liposomal cytarabine) which can be delivered with manageable toxicity.[48]

Future strategies

Specifically targeted chemotherapies targeting oncogenic pathways are a promising future application of molecular subgrouping. Currently, molecularly targeted agents for each of the four molecular subgroups are being evaluated in preclinical and clinical models. The most well-studied of these is Vismodegib, that has demonstrated some utility in both preclinical and clinical models and may be an option in adolescents and older children.[49]

Alternative strategies include sensitization of MB tumor cells to chemotherapeutic treatment. Thiostrepton, an antagonist of *FOXM1* (an oncogene known to be

upregulated in a variety of malignancies), was shown to sensitize MB cells to cisplatin *in vitro*.[50]

In our setting, future strategies must focus on improving access to molecular classification which is the cornerstone for improving outcomes and limiting toxicity. For example, infant SHH even with metastasis may be curable using chemotherapy only approaches and WNT tumors may be offered reduced dose CSI. It is therefore, imperative that ongoing efforts in LMIC focus on this. Till genomic profiling becomes more widely available, validation, and incorporation of IHC and radiogenomics could play a major role in delievering risk-adapted treatments aimed at optimizing outcomes and limiting toxicity.

Summary and Recommendations

- Optimal treatment of MB can yield high cure rates even in countries with limited resources
- The current risk stratification incorporates clinical, histopathological and molecular characteristics
- Molecular characterization, while of immense prognostic and therapeutic significance may not be feasible for the vast majority of patients in our setting
- Immunohistochemistry-based approach to molecular characterization may offer a pragmatic approach
- Optimal resection is the cornerstone of treatment. However, in view of the radio and chemo-sensitivity of the tumor, heroic attempts at complete resection associated with neurological morbidity are unwarranted
- Placement of VP shunts is not required and temporary diversion measures should suffice in cases with marked hydrocephalus
- Radiation is an essential part of treatment in older children. It should be or omitted/deferred in younger children wherever feasible. Tumor bed boost is equivalent to posterior fossa boost
- Current evidence supports adjuvant chemotherapy in all patients for 6–8 cycles. High-dose chemotherapy may offer an advantage in salvage settings
- Ongoing approaches are focused on improving outcomes for high risk disease and limiting the late effects associated with treatment
- For LMIC these should be focused on improving access to molecular stratification.

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Conflicts of interest

There are no conflicts of interest.

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