Paediatric Medulloblastoma: An Updated Review

SJ Taran[1], R Taran[2], N Malipatil[3], K Haridas[4]

ABSTRACT

Medulloblastoma is one of the most common malignant tumours of the central nervous system in children. It affects two persons per million per year worldwide and is increasing. More than 70% of patients diagnosed with medulloblastoma are predominantly below age 10 years. Histological variants of medulloblastoma are recognized as classic, nodular-desmoplastic, large cell/anaplastic and medulloblastoma with extensive nodularity. Symptoms include headache, general malaise, failure to feed, vomiting, clumsiness and other presentations that mimic common and benign childhood pathologies seen in primary care. Study data suggested an inverse correlation between high-stage disease and duration of symptoms. Currently, medulloblastoma is classified clinically into high risk and standard (average) risk depending upon factors solely clinical – age, metastases and resection. The treatment strategies for medulloblastoma are maximal safe resection (plus/minus cerebrospinal fluid diversion), neuraxis radiotherapy and chemotherapy. Medulloblastoma is the first brain tumour to show efficacy of chemotherapy in large prospective trials. Effective chemotherapy regimens remain elusive for almost all patients with high-grade cortical or brainstem gliomas and for most young patients with residual or metastatic disease of any histology. Conventional chemotherapeutic agents continue to be developed to reduce toxicity and/or improve efficacy. Recent advances in tumour biology have changed the emphasis to novel agents that target molecular changes crucial for tumour proliferation or survival. The toxicity and efficacy of several of these novel agents are currently being assessed in children with brain tumours.

Keywords: Medulloblastoma, paediatric medulloblastoma, primitive neuroectodermal tumour (PNET)

Meduloblastoma pediátrico: una revisión actualizada

SJ Taran[1], R Taran[2], N Malipatil[3], K Haridas[4]

RESUMEN

El meduloblastoma es uno de los tumores malignos más comunes del sistema nervioso central en los niños. Representa alreadedor de 2 personas por millón por año a nivel mundial y va en aumento. Más del 70% de los pacientes diagnosticados con meduloblastoma corresponden poseen predominantemente edades por debajo de los 10 años. Las variantes histológicas del meduloblastoma son clasificadas como clásicas, nodular-desmoplásicas, células anaplásicas grandes, y meduloblastomas con nodularidad extensa. Los síntomas incluyen dolor de cabeza, malestar general, falta de apetito, vómitos, torpeza, y otras manifestaciones que semejan patologías comunes y benignas de la infancia observadas en la atención primaria. Los datos del estudio sugieren una correlación inversa entre la enfermedad en su estapa alta y la duración de los síntomas. En la actualidad, el meduloblastoma se clasifica clínicamente como de alto riesgo o de riesgo estándar (promedio) dependiendo de factores exclusivamente clínicos – edad, metástasis y resección. Las estrategias de tratamiento para el meduloblastoma son la resección máxima segura (más/menos derivación del LCR), radioterapia neuraxial, y quimioterapia. El meduloblastoma es el primer tumor cerebral que demuestra la eficacia de la quimioterapia en grandes ensayos prospectivos. Los regímenes de quimioterapia eficaz siguen sin lograr soluciones duraderas en casi todos los pacientes con

From: [1]Department of Pediatrics, [2]Department of Medical Oncology, Sri Aurobindo Institute of Medical Sciences, Sanwar Road, Indore-452015, India, [3]Family Physician, No 206, Nithyashree Sankalp Apartments, Subramanyapura Main Road, Bangalore- 560061, India and [4]Clinical Pharmacologist, Bangalore, India.

Correspondence: Dr N Malipatil, Family Physician, No 206, Nithyashree Sankalp Apartments, Subramanyapura Main Road, Bangalore- 560061, India. E-mail: nagaraj.malipatil@gmail.com

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gliomas de alto grado corticales o del tronco encefálico, y en la mayoría de los pacientes jóvenes con enfermedad residual o metastásica de cualquier histología. Los agentes quimioterápicos convencionales ccontinuan siendo desarrollados con el fin de reducir la toxicidad y mejorar la eficacia. Los avances recientes en biología tumoral han cambiado el énfasis hacia nuevos agentes dirigidos a cambios moleculares cruciales para la proliferación tumoral o la supervivencia. La toxicidad y la eficacia de varios de estos nuevos agentes están siendo actualmente evaluadas en niños con tumores cerebrales.

Palabras claves: meduloblastoma, meduloblastoma pediátrico, tumor neuroectodérmico primitivo (TNEP)

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INTRODUCTION

Medulloblastoma is one of the most common types of malignant brain tumours in childhood (1). It belongs to the group of tumours known as primitive neuroectodermal tumours (PNET), which are highly malignant, small round blue cell tumours of the central nervous system (1).

Epidemiology

Medulloblastomas affect just under two people per million per year, worldwide (2). It occurs more frequently in males (ratio 1.5:1) and usually before 10 years of age. Although much less common, the disease may also occur in adults, usually in the 3rd and 4th decades of life (2). Forty per cent of medulloblastoma patients are diagnosed before the age of five years, 31% are between the ages of five and nine years, 18.3% are between the ages of 10 and 14 years, and 12.7% are between the ages of 15 and 19 years (2).

Multi-institutional data on central nervous system tumours in the paediatric age group (< 18 years of age) collected from the neuropathology records of seven tertiary hospitals in India report medulloblastoma as the most common brain tumour in the paediatric age group, preceded only by astrocytoma (3). The incidence of paediatric posterior fossa medulloblastoma is higher in the first decade of life, and there is a well-known male predominance (3).

Pathology

The cell of origin of medulloblastoma is still controversial. It has been speculated that it arises from cells of the external granular layer of the cerebellum or from undifferentiated cells of the posterior medullary velum. Four histological variants of medulloblastoma are recognized: classic, nodular-desmoplastic, large cell/anaplastic and medulloblastoma with extensive nodularity (4).

Classic medulloblastoma (the majority) is a highly cellular tumour composed of diffuse masses of small, undifferentiated oval or round cells. Desmoplasmic/nodular medulloblastoma is called nodular because of its architecture and desmoplastic because it is permeated by fine collagen (reticulin) fibres that give it a firm consistency. Desmoplasmic/nodular medulloblastoma is more common in infants and may have a better prognosis than the classic form. Medulloblastoma with extensive nodularity may be difficult to distinguish from nodular/desmoplastic. It occurs also in infants and has a good prognosis. Another variant, large cell/anaplastic medulloblastoma shows large anaplastic nuclei with a high rate of mitosis and apoptosis. This variant has poor prognosis. Distinct molecular signatures correspond to some of these clinicopathological phenotypes [Table 1] (4).

Table 1: Distinct molecular signatures of medulloblastoma correspond to clinicopathological phenotypes

Molecular pathway	WNT	SHH	Group 3	Group 4
Genes involved	Beta-catenin mutation, monosomy 6	PTCH1 deletion, SUFU deletion, MYCN overexpression	MYCN amplification isochromosome 17q	Isochromosome 17q
Clinical profile	Older children and adults, good prognosis	Infants, children and adults, good to intermediate prognosis	Infants and children, poor prognosis	Older children and adults, the most common form, intermediate prognosis
Tumour location	Fourth ventricle, infiltration of dorsal brainstem	Cerebellar hemispheres	Cerebellum NOS	Cerebellum NOS
Histology	Classic	Desmoplastic, classic, LCA	Classic, LCA	Classic, LCA
Cell of origin	Precursors around the fourth ventricle	EGL	NA	NA
Tumour syndrome	Turcot	Gorlin	None	None

The genesis of medulloblastoma is driven by genetic pathways that are also involved in the development of the cerebellum. Abnormalities in these pathways convert stem cells to tumour cells. Four molecular subtypes of medulloblastoma have been described. Two of these subtypes, involving the wingless pathway tumours and the sonic hedgehog pathway have been defined in greater detail, and the other two are less well understood. The main features of these are partially listed in Table 1. These groups are not homogeneous in their clinical and pathological phenotypes. In the future, molecular charac-

terization may lead to personalized therapy for these tumours (4).

Clinical features

The clinical features of medulloblastoma, as with other posterior fossa pathology, can be difficult to detect initially in young children, sometimes leading to a delayed diagnosis (5). Symptoms include headache, general malaise, failure to feed, vomiting, clumsiness and other presentations that mimic common and benign childhood pathologies seen in primary care (5). Halperin *et al* reported a median duration of presenting symptoms of four weeks in children < 3 years of age with medulloblastoma; in older children, the corresponding figure was eight weeks. A higher rate of high-stage disease was found in patients < 36 months of age compared with those aged > 36 months [47% *versus* 36%, respectively] (6). These data suggested an inverse correlation between high-stage disease and duration of symptoms. Young children with aggressive medulloblastoma are more likely to be diagnosed earlier than older children despite their inability to verbalize symptoms (6).

Management

Typically, the treatment strategies for medulloblastoma are threefold: maximal safe resection (plus/minus cerebrospinal fluid diversion), neuraxis radiotherapy and chemotherapy (7). Survival in children with medulloblastoma has improved over the last 20 years, and the quality of life in medulloblastoma survivors has been evaluated in terms of physical and non-physical impairments (8). Physical impairments include neurological deficits, secondary malignancy and endocrine dysfunction, whereas non-physical deficits include cognitive difficulties and psychological and social problems (9). The effect of these problems can be far reaching, affecting employment and family life (10−12). Many long-term sequelae are secondary to radiotherapy and one of the goals of modern therapy is to minimize or avoid radiotherapy (10, 11).

Very young children (generally defined as those less than three years of age) with brain tumours continue to pose a unique therapeutic challenge. Craniospinal irradiation is typically not administered to them because of the devastating neurocognitive sequelae associated with its use (11). This limitation in therapy and the distinct biological characteristics of these tumours are likely reasons children less than three years old with embryonal tumours generally have a poor prognosis despite very aggressive treatment (11). However, for selected subgroups of patients, most notably those with localized, completely resected medulloblastoma, survival has improved.

Risk stratification

Medulloblastoma was classified clinically by Chang in 1969 based on the size and invasiveness of the tumour as determined intra-operatively and on the presence of metastases (12). The Chang system is no longer used, although elements of it from the current clinical risk stratification of medulloblastoma are applied (12). Currently, medulloblastoma is classified clinically into high risk and standard (average) risk, which is summarized in Table 2. The factors contributing to this classification are solely clinical – age, metastases and resection (5). Age is a key factor, which may reflect in part the aggressive natural history of tumours in the under-three years age group and also reflect the limitations and side effects of therapy.

Table 2: Established prognostic variables accepted by the North American Children's Oncology Group and the International Society of Pediatric Oncology Group (5, 12)

Risk classification	Characteristics
Standard-risk tumour	≥ 3 years of age without evidence of metastatic spread and having ≤ 1.5 cm^2 (maximum cross-sectional area) of residual disease after surgery
High-risk tumour	≥ 3 years of age with evidence of cerebrospinal spread (M1–M3) and/or those with less complete resection (≥ 1.5 cm^2) or < 3 years of age at diagnosis

Older children with medulloblastoma

The cure rates for children and young adults diagnosed with medulloblastoma have improved significantly in the past three decades [Table 3] (13). Improved ability to perform gross total resections, introduction of magnetic resonance imaging to accurately stage patients, advanced techniques to deliver radiation therapy and improved supportive care have all contributed to this success, but the introduction of chemotherapy has played a key role.

The first randomized study [CCG 9892] (14) that suggested the efficacy of chemotherapy in medulloblastoma treated all patients with 36 Gy CSI with a boost to the posterior fossa of 54 Gy and weekly vincristine during radiation therapy. This was supported by the first International Society of Pediatric Oncology (SIOP) trial with a similar study design (15). However, due to the deleterious neurocognitive and neuroendocrine consequences associated with this treatment, the next generation of cooperative group studies tested the efficacy of reduced CSI dose for patients with average-risk disease. Patients with gross total resections and no metastatic disease (M0R0) were categorized as having average-risk disease.

The greater toxicity associated with higher-dose CSI (36 Gy to the craniospinal axis and 54 Gy to the posterior fossa) and the equivalent disease control achieved using adjuvant chemotherapy (lomustine, cisplatin and vincristine) and reduced-dose CSI (23.4 Gy to the craniospinal axis and 54 Gy to the posterior fossa) in randomized Pediatric Oncology Group (POG) and the Children's Cancer Group (CCG) studies (15) support the use of reduced-dose CSI together with chemotherapy as the new "standard" for therapy in children with medulloblastoma. Evaluation is under progress by the current Children's Oncology Group to further reduce the dose of CSI to 18 Gy while maintaining the same degree of disease control (14, 15).

Recently concluded studies from Europe have attempted

Table 3: Prospective clinical trial results for older children with average-risk and high-risk medulloblastoma

Trial	n	Treatment	Radiotherapy dose CSI	Radiotherapy dose PF	Five-year EFS (± SE)*	Ref
Average risk (M0R0)						
CCG 9892 (1990–1994)	65	Reduced-dose RT with weekly VCR followed by CHT (VCR, CDDP, and CCNU)	23.4 Gy 55.8 Gy		78 ± 5%	14
SIOP-PNET3 (1992–2000)	179	Standard-dose RT only vs pre-RT CHT (VCR, VP-16, CBDA, & Cyclo)	35 Gy	55 Gy	60% *vs* 74% $p = 0.036$	15
HIT-91 (1991–1997)	118	Pre-RT CHT (ifos, ara-C, VP-16, HD-MTX, CDDP) vs Post-RT CHT (VCR, CDDP, and CCNU)	35.2 Gy 55.2 Gy		65 ± 5% *vs* 78 ± 6% (3-y EFS) $p = 0.03$	16
A9961 (1996–2000)	383	Weekly VCR during RT, then CCNU, CDDP, VCR vs cyclo, CDDP, VCR	23.4 Gy	55.8 Gy	82 ± 3% *vs* 80 ± 3%	17
SJMB96 (1996–2003)	86	Reduced-dose RT followed by 4 cycles of high-dose CHT with ASCR (VCR, CDDP, and cyclo)	23.4 Gy	55.8 Gy	83% (95% CI, 73–93)	18
High risk (M1–M3 ± R1) HIT-91 (M2–M3) (1991–1997)	19	As above (separate results for the 2 treatment arms were not provided)	35.2 Gy	55.2 Gy	30 ± 15% (3-y EFS)	16
SIOP-PNET3 (M2–M3) (1992–2000)	68	Pre-RT CHT (VP-16 VCR, cyclo, and CBDA)	35 Gy	55 Gy	34.7%	19
CHOP (M1–M3)	15	Weekly VCR during RT, then CCNU, CDDP, VCR	36 Gy	55.8 Gy	67 ± 15%	20
SJMB96 (M1–M3)	48	Topotecan window pre-RT followed by 4 cycles of high-dose CHT with ASCR (VCR, CDDP, and cyclo)	36–39.6 Gy	55.8 Gy	70% (95% CI, 55–85)	18

Ara-C; cytosine arabinoside; ASCR; autologous stem cell rescue; CBDA; carboplatinum; CCNU; lomustine; CDDP; cisplatin; CHT; chemotherapy; CSI; craniospinal irradiation; Cyclo; cyclophosphamide; EFS; event-free survival; ifos; ifosphamide; HD-MTX; high dose methotrexate; PF; posterior fossa; RD; residual disease; ref; reference; RT; radiation therapy; VCR; vincristine; VP-16; etoposide; 8-in-1; 8 chemotherapeutic agents administered in one day (consisting of VCR; methylprednisolone; CCNU; CDDP; hydroxyurea; procarbazine; ara-c; and cyclo). *Unless otherwise stated.

to answer the question of timing of chemotherapy in relation to radiotherapy. The SIOP III study confirmed that postoperative standard-dose CSI alone achieves five-year event-free survival rates of between 60% and 65% and that this can be improved with the addition of platinum-based chemotherapy (15).

The HIT ’91 trial demonstrated that the addition of adjuvant chemotherapy has improved the cure rates for average-risk medulloblastoma. Current protocols are testing the feasibility of further reduction in the dose of CSI (16).

Very young children with medulloblastoma

The realization in the 1980s that CSI results in devastating consequences on the developing central nervous system of very young children prompted investigators to devise strategies to avoid or delay CSI for this group of children. During the 1990s, several studies were conducted to address this issue (Table 4). The POG and CCG adopted a delayed radiotherapy approach in the POG 8633/34 [termed Baby POG-1] (21, 22) and CCG 921 trials (22). In Baby POG-1, children under the age of three years were treated with chemotherapy consisting of vincristine, cyclophosphamide, etoposide and cisplatin. Depending on patient age, CSI was delivered at one or two years post-diagnosis. Using this approach, CSI was successfully delayed in only 40% of patients. The five-year progression-free survival and overall survival for all medulloblastoma patients were 31.8 ± 8.3% and 39.7 ± 6.9% respectively. Of note, medulloblastoma patients with non-metastatic and gross totally resected tumour (M0R0) had much better outcomes, with five-year OS of 69%. In an attempt to improve outcome, the succeeding POG study 9233/34 [termed Baby POG-2] (23) intensified the chemotherapy regimen. Patients were randomized between standard Baby POG-1 treatment or an intensified version of Baby POG-1 therapy in which the same drugs were administered at higher doses and more frequently. No difference in EFS or OS was observed between patients receiving standard or intensified Baby POG therapy (23). This strategy was adopted and confirmed in the CCG 9921 trial in a subset of medulloblastoma patients younger than three years of age at diagnosis.

To avoid CSI, German investigators used a strategy of high-dose systemic and intensive intraventricular methotrexate combined with standard chemotherapy (25). Using this approach, the HITSKK92 trial achieved the best results to date for children less than three years old with M0/M1R0 medulloblastoma (n = 17), with five-year PFS of 82 ± 9% and OS of 93 ± 6%. Additionally, the mean IQ of survivors, although higher than historical controls that received whole brain radiotherapy, was significantly lower than that of age-matched controls (21). This study revealed that the majority of young children without macroscopic metastasis and completely resected medulloblastoma can be cured with chemotherapy alone, but at a cost of methotrexate-induced neurotoxicity.

The use of myeloablative chemotherapy with autologous stem cell rescue has also been investigated as an alternative to

CSI. This approach was used by the Head Start II trial, and has achieved the best results to date for young children (defined as age less than six years in this trial) with metastatic medulloblastoma [M1–M3] (n = 21), with three-year EFS of 49% (95% CI 27%, 72%) and OS of 60% [95% CI, 36%, 84%] (27).

On the basis of the Head Start regimen, the CCG tested the feasibility of delivering multiple courses of myeloablative chemotherapy with ASCR (termed tandem transplants) as part of the CCG 99703 trial (n = 21). Patients younger than three years of age received three cycles of intensive standard chemotherapy followed by three cycles of myeloablative chemotherapy with ASCR. Results are pending (26).

Recent improvements in radiotherapy delivery techniques, permitting more precise tumour targeting, have generated renewed interest in the use of focal radiotherapy for very young patients with localized disease. This strategy has been implemented in two recent trials: the COG P9934 study and the PBTC-001 study. The COG P9934 included focal radiotherapy after 16 weeks of induction chemotherapy for patients with M0R0 medulloblastoma. In the PBTC-001 study, patients received standard chemotherapy plus intrathecal mafosfamide for 20 weeks, followed by focal radiotherapy and then 20 weeks of maintenance chemotherapy. Results from these trials are also pending (24−27).

Table 4: Results of prospective clinical trials for infants and young children with medulloblastoma

Trial	n	Five-year Event-free survival (% ± SE)*	Five-year overall survival (% ± SE)*	Reference
M0R0				
Baby POG	13		69	21, 22
CCG 9921	38	41 ± 8	54 ± 8	23
SFOP	47	29 (95% CI 18, 44)	73 (95% CI 59, 84)	24
HIT-SKK92	17	82 ± 9	93 ± 6	25
Head Start I+II (age < 3 years)	14	64 ± 13	86 ± 9	26
M0R1				
CCG 9921	23	26 ± 9	40 ± 11	23
SFOP	17	6 (95% CI 1, 27)	41 (95% CI 22, 64)	24
HIT-SKK92	14	50 ± 13	56 ± 14	25
Head Start I+II (age < 3 years)	7	29 ± 17	57 ± 19	26
Metastatic (M+)				
CCG 9921	31	25 ± 8	31 ± 9	23
SFOP	15	13 (95% CI 4, 38)	13 (95% CI 4, 38)	24
HIT-SKK92	12	33 ± 14	38 ± 15	25
Head Start II (age < 6 years)	21	3-y EFS 49 (95% CI 27, 72)	3-y OS 60 (95% CI	27

CI: confidence interval; SE: standard error; EFS: event-free survival; OS: overall survival.

CONCLUSION

While surgery and radiotherapy are the mainstay of therapy for older children with medulloblastoma, chemotherapy has also played a key role. Medulloblastoma is the first brain tumour to show efficacy of chemotherapy in large prospective trials. On the other hand, many children with brain tumours remain incurable with current therapies. Effective chemotherapy regimens remain elusive for almost all patients with high-grade cortical or brainstem gliomas and for most young patients with residual or metastatic disease of any histology. In the past three decades, chemotherapeutic agents have been extensively evaluated for the treatment of brain tumours in a myriad of schedules, doses and combinations. A plateau in efficacy has been reached. Further treatment intensification using conventional nonspecific chemotherapy is more likely to result in additional toxicity without major advances in survival. Modest improvements in outcome may be achieved by further refining treatment schedules and introducing new chemotherapeutic agents.

Although conventional chemotherapeutic agents continue to be developed to reduce toxicity and/or improve efficacy, the remarkable advances made in knowledge of tumour biology in the past decade have shifted the focus novel agents that target molecular changes crucial for tumour proliferation or survival. These selective agents are predicted to be less toxic to normal cells and it is anticipated that they will be more effective than currently used nonspecific chemotherapeutic agents. The toxicity and efficacy of several of these novel agents are currently being assessed in children with brain tumours. Ultimately, if these novel therapies prove effective, their role in combination with established chemotherapeutic agents will need to be assessed.

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