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REVIEW ARTICLE

# The Management of Children with Pre-School Medulloblastoma – A Review of Four Decades of Multi-Disciplinary and Multi-Institutional Collaboration.

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## ABSTRACT

**Background**: The management and consequent survival and quality of survival for young children with medulloblastoma have undergone substantial improvement over the last four decades. While many of these changes reflect improvements in pediatric neurosurgical, neuro-imaging and radiation oncologic technology and training, as well as in supportive care experience and expertise, this review will focus particularly upon improvements in chemotherapeutic approaches.

**Methods**: This review focuses only upon prospective clinical trials conducted in young children with newly-diagnosed medulloblastoma since the 1980s. The upper age limits for these trials varied from under three to up to six years of age at diagnosis.

**Results**: Certain but not all trials endeavoring to improve outcomes for young children with now-recognized pathological and molecular low-risk characteristics, specifically the Sonic Hedgehog sub-type, representing some 50-60% of young children with medulloblastoma, have reaped substantial gains in event-free and overall survival, irradiation-free survival as well as neuropsychological outcomes. Those successful trials utilized either induction including intravenous high-dose methotrexate and intraventricular (intra-Ommaya) methotrexate without consolidation by marrow-ablative chemotherapy with autologous hematopoietic progenitor cell rescue, or induction with or without intravenous high-dose methotrexate (but not intra-ventricular methotrexate) followed by consolidation with marrow-ablative chemotherapy with autologous hematopoietic progenitor cell rescue. These two approaches have consistently produced superior outcomes compared with other trials. For children with molecularly-characterized Groups 3 or 4 medulloblastoma, representing those at high-risk of relapse, some modest improvements have been made over the years, but much room for improvement remains, especially for those presenting with the highest-risk molecular characteristics (Group 3 medulloblastoma) as well as for children with metastatic disease at initial diagnosis.

**Conclusions**: Substantial gains in improving outcomes for young children with medulloblastoma have been achieved with acceptable short- and long-term morbidities of treatment. However, the inclusion of intra-ventricular therapies (conventional chemotherapeutic, radio-labeled monoclonal antibody or adaptive cellular immunotherapeutic approaches) as well as the identification of targeted systemic therapies (biological and/or immunological) and their incorporation into prospective multi-center clinical trials, must be investigated prospectively if we are to improve outcomes for those children at high-risk for relapse, even with the inclusion of refined irradiation therapeutic approaches.

**Keywords**: medulloblastoma, chemotherapy, young children, newly-diagnosed.

## Introduction

By early to mid-1980s, it had become clear to pediatric oncologists that outcomes for the youngest of children (then considered less than three years of age at diagnosis) produced miserable survival and quality of life outcomes, even with the use of full-dose cranio-spinal irradiation[1,2]. Through the 1970s to early 1990s, historically, between zero and, at best, 34% of young children with medulloblastoma were surviving without tumor recurrence at two to five years from diagnosis, in the USA, British, French and German studies - on average, about 23%. Of note, the average time from diagnosis to relapse in most of these early trials was between six and nine months.

Three trials were therefore initiated and conducted sequentially by the Pediatric Oncology Group (POG; "Baby POG" I and II) to attempt to *delay* irradiation[3-5]. The POG also conducted a trial (P9934) for non-metastatic medulloblastoma utilizing four months of chemotherapy (without methotrexate) followed by focal irradiation[6].

Two trials by the Children's Cancer Group (CCG-921 and CCG-9921) attempted to *avoid* irradiation[7-10], both using prolonged intravenous multi-agent chemotherapy. Additionally, the French Society of Paediatric Oncology (SFOP) conducted a prospective multi-center "baby" brain (BB) trial of chemotherapy alone (BBSFOP) wherein they evaluated multi-agent chemotherapy with the intent to avoid irradiation until patients relapsed[11].

The German HirnTumor Sauglinge und KleinKinder (HIT-SKK) trials added intravenous high-dose methotrexate and intra-ventricular methotrexate to standard chemotherapy, initially with delayed irradiation and subsequently with elimination of irradiation[12-15]. The United Kingdom Children's Cancer Group (UKCCSG) and International Society of Paediatric Oncology (SIOP) trial CNS9204 also incorporated intravenous high-dose methotrexate without intra-ventricular methotrexate into their co-operative trial[16]. Additionally, the Children's Oncology Group (COG, formerly CCG) conducted a trial in children with non-metastatic desmoplastic/ nodular medulloblastoma (ACNS1221), in which an attempt was undertaken to replicate the favorable results of the HIT-SKK trials without inclusion of intra-ventricular methotrexate[17].

"Head Start" Consortium has initiated, conducted, and completed three sequential irradiation-avoiding chemotherapy regimens for children with medulloblastoma under six years of age at diagnosis ("pre-school" children) between 1990 and 2009[18-21]. These "Head Start" trials all included induction chemotherapy (without or subsequently with high-dose methotrexate) followed by a single cycle of marrow-ablative chemotherapy and autologous hematopoietic progenitor cell rescue (AuHPCR).

COG conducted a phase I/II trial of initial chemotherapy (without high-dose methotrexate) followed by three tandem cycles of marrow-ablative chemotherapy with thiotepa/carboplatin and AuHPCR (CCG-99703)[22]. This led to the development of the COG trial ACNS0334, in which children under three years of age with clinically high-risk medulloblastoma (metastatic or residual primary site disease) received three cycles of "Head Start"-like induction chemotherapy randomized to receive or not receive high-

dose methotrexate, followed by three sequential cycles of high-dose chemotherapy with AuHPCR, similar to CCG99703 (preliminary outcomes data presented but not yet published)[23]. Additionally, "Head Start" 4 was initiated in 2014, in which infants and young children with low-risk medulloblastoma (SHH or Wnt) under six years of age were assigned three or five induction cycles of "Head Start" II chemotherapy based on response followed by a single cycle of marrow-ablative chemotherapy with AuHPCR. Patients with high-risk medulloblastoma (Groups 3 and 4) less than 10 years of age were randomized following three or five induction cycles to receive either single cycle marrow-ablative chemotherapy with AuHPCR or three tandem cycles; this trial met accrual goals in February 2024 and is now closed to further accrual pending eligibility and evaluability review.

The North American Pediatric Brain Tumor Consortium (PBTC) sequentially conducted two trials, a phase 1 trial of intrathecal mafosfamide[24], followed by a phase II trial with intrathecal mafosfamide and systemic chemotherapy (without methotrexate) and conformal irradiation for children less than three years of age[25]. The PBTC has since conducted the first prospective clinical trial incorporating biological agents, vorinostat and isotretinoin, into the treatment of newly-diagnosed children less than four years of age without either methotrexate or marrow-ablative chemotherapy[26].

Finally, the most recently published trial (SJYC07) from the St. Jude Children's Research Hospital and their collaborating institutions employed high-dose methotrexate in induction, but neither intraventricular methotrexate nor marrow-ablative chemotherapy[27]. Currently, St. Jude is conducting the SJiMB21 trial, a phase II study of molecular and clinical risk-directed therapy for young children less than five years old with newly-diagnosed medulloblastoma.

The management strategies of each of these trials, and subsequent outcomes (for completed and published trials), including neuropsychological and quality of life outcome measures, will be comprehensively detailed. The goals of currently open clinical trials for young children with medulloblastoma will also be described and discussed.

## Methods:

A comprehensive review of published (hard copy print or online), peer-reviewed, prospective clinical trials from 1980 onwards, involving patients with newly diagnosed medulloblastoma, was conducted. This review focused on young children aged under three to six years at diagnosis, some were treated as a component of particularly earlier trials in which older children were included. Clinical trials conducted in North America, Europe and Australasia were included. Prospective trials that are currently ongoing have been detailed. Review articles and published abstracts of completed trials based upon oral or poster presentations have been largely excluded, in scenarios where the trial outcomes have not yet been primarily published. Manuscripts that were in preparation or in press at the time of preparation and submission of this manuscript have been excluded.

Quantitative trial data have been tabulated in a systematic manner to differentiate protocols

used in the management of these young children. Qualitative trial data, including neuropsychological and quality of life outcomes, have been comprehensively described within the manuscript. High-risk disease included any metastatic disease (M+) or any residual tumor (R+), considering the variation across studies in defining and integrating "high-risk" disease data into their analyses.

## Results:

This review highlights the prospective clinical trials focusing on management of young children diagnosed with medulloblastoma. Table 1 summarizes the major trials conducted and published for newly-diagnosed medulloblastoma, grouped by consortia.

**Table 1:** Clinical trials for newly diagnosed medulloblastoma in young children, grouped by consortia

| Trials | Years conducted | Author | Year published |
|---|---|---|---|
| The Pediatric Oncology Group (POG) trial "Baby POG" I | 1986 to 1990 | Duffner et al | 1993 |
| The Pediatric Oncology Group (POG) trial "Baby POG" II | 1992 to 1998 | Strother et al | 2015 |
| The Société Française d'Oncologie Pédiatrique (SFOP) trial BBSFOP | 1990 to 2002 | Grill et al | 2005 |
| The United Kingdom Children's Cancer Group (UKCCSG) and International Society of Paediatric Oncology (SIOP) co-operative trial CNS 9204 | 1993 to 2003 | Grundy et al | 2010 |
| The Australian/New Zealand Children's Hematology Oncology Group trial ANZCCSG BabyBrain99 | 1999 to 2005 | Bandopadhayay et al | 2011 |
| The Children's Cancer Group (CCG) trial CCG-921 | 1986 to 1992 | Geyer et al, Zeltzer et al | 1994 1999 |
| The Children's Cancer Group (CCG) trial CCG-9921 | 1993 to 1997 | Geyer et al Leary et al | 2005 2011 |
| The Children's Cancer Group (CCG) trial CCG-99703 | 1998 to 2004 | Cohen et al | 2015 |
| The Children's Oncology Group (COG) trial P9934 | 2000 to 2006 | Ashley et al | 2012 |
| The Children's Oncology Group (COG) trial ACNS0334* | 2007 to 2014 | Mazewski et al | 2020 |

| Trials | Years conducted | Author | Year published |
|---|---|---|---|
| The Children's Oncology Group (COG) trial ACNS1221 | 2013 to 2016 | Lafay-Cousin et al | 2020 |
| The Pediatric Brain Tumor Consortium (PBTC) trial PBTC-001 | 2001 to 2005 | Blaney et al | 2012 |
| The Pediatric Brain Tumor Consortium (PBTC) trial PBTC-026 | 2009 to 2014 | Leary et al | 2022 |
| The HirnTumor Sauglinge und KleinKinder (HIT-SKK) trial HIT-SKK'87 | 1987 to 1993 | Rutkowski et al | 2009 |
| The HirnTumor Sauglinge und KleinKinder (HIT-SKK) trial HIT-SKK'92 | 1992 to 1997 | Rutkowski et al | 2005 |
| The HirnTumor Sauglinge und KleinKinder (HIT-SKK) trial HIT-SKK'00 | 2001 to 2005 | von Bueren et al | 2011 |
| The HirnTumor Sauglinge und KleinKinder (HIT-SKK) trial HIT-SKK'BIS4 | 2001 to 2011 | Myranek et al | 2020 |
| The "Head Start" Consortium trial "Head Start" I | 1990 to 1995 | Mason et al, Dhall et al | 1998. 2008 |
| The "Head Start" Consortium trial "Head Start" II | 1997 to 2003 | Chi et al, Dhall et al | 2004, 2008 |
| The "Head Start" Consortium trial "Head Start" III | 2003 to 2009 | Dhall et al | 2020 |
| The "Head Start" Consortium trial "Head Start" IV** | 2015 till date | NA | NA |
| The St. Jude Children's Research hospital trial SJYC07 | 2007 to 2017 | Robinson et al | 2018 |
| The St. Jude Children's Research hospital trial SJiMB21** | 2022 till date | NA | NA |

*abstract only

** ongoing trial

NA: not applicable

Baby POG I and II trials spanned from 1986 to 1998 (Table 2)[4,5]. These two trials contained 24% to 40% of patients with metastatic disease and approximately 60% of patients with localized residual tumor. Baby POG I enrolled 62 patients below three years of age, of whom 69% patients were below two years of age. The induction regimen included vincristine, high-dose cyclophosphamide, cisplatin and etoposide, with therapy spanning 24 months for patients less than two years of age, or 12 months for patients between two to three years of age at diagnosis. Craniospinal irradiation (CSI) was modified as per disease status from 24 Gray (Gy; disease-free) to 35.2 Gy (residual or

metastatic disease); the posterior fossa irradiation boost was also modified from 50 Gy (disease-free) to 54 Gy (residual or metastatic disease). The 2-year progression-free survival (PFS) and overall survival (OS) was 34% and 46%, respectively, for all patients. The Baby POG I study highlighted favorable prognostic factors such as gross total resection, complete response to chemotherapy and localized disease. Cognitive tests were performed at baseline and one-year post-chemotherapy completion and the study did not find decline in cognitive scores.[4] Baby POG II trial enrolled 112 patients below three years of age and was designed as a randomized trial to test if dose intensification of the Baby POG I regimen would result in improved survival as seen in other solid tumors. The chemotherapy in the "experimental" study arm (1.8 times more dose intense than the Baby POG I at 21-day cycles) led to a 20% cure rate with chemotherapy alone but did not improve the 2-year PFS (27%); on the contrary, it did result in increased toxicity and mortality[5].

P9934 trial was conducted by COG from 2000 to 2006 (Table 2)[6]. This trial enrolled 74 patients below age three years, all of whom had non-metastatic tumors, and 31% patients had residual tumor. The induction chemotherapy regimen spanned 4 months, with each cycle given over 4 weeks and comprising of cisplatin and vincristine, followed by cyclophosphamide, followed by oral etoposide as a 21-day maintenance therapy. Afterwards, second-look surgery was offered for patients with residual tumor, followed by conformal irradiation offered to patients without tumor progression, with dosing adjusted to age and treatment response (18 or 23.4 Gy to posterior fossa and total tumor bed dose of 50.4 or 54 Gy). Maintenance chemotherapy regimen spanned over 8 months and involved a 28-day cycle of cyclophosphamide and vincristine, followed by a 28-day cycle of oral etoposide given for 21 days, with the 2-cycle course repeating 4 times. The 4-year PFS for all patients was 50%, for patients with residual tumor was 39% and those with desmoplasia/ nodular subtype was 58%. Treatment related death was noted in one patient during induction. Neurodevelopmental outcome data did not show declining cognitive or motor outcome[6].

CCG-921 and CCG-9921 trials were conducted between 1986 and 1997 (Table 2)[7-10]. The CCG-921 study enrolled 46 infants below 18 months of age (30% with metastatic disease, 50% of 34 patients with residual tumor) and 19 patients aged 18 months to three years. The protocol for infants (less than 18 months) and younger children (18 months to three years) involved induction with two cycles of "eight-drugs-in-one-day" chemotherapy regimen administered two weeks apart, followed by eight cycles of maintenance regimen of the "eight-drugs-in-one-day" chemotherapy given every six weeks. For infants, the application of radiation therapy was optional, to be used as focal irradiation after two cycles of induction chemotherapy or as CSI at the end of maintenance chemotherapy. For children aged 18 months to three years, the qualifying age for radiation therapy (optional) was raised sequentially to two years and later to three years during the early course of the study; for such patients, the entire chemotherapy protocol was to be followed by both delayed

and reduced-dose irradiation of 45 Gy to the primary tumor site and 23.4 Gy to the craniospinal axis. Infants had a poor 3-year PFS of 22%, with a subset of these patients (with localized and non-residual tumor) having 3-year PFS of 33%. The children aged 18 months to three years also fared poorly, with a 5-year PFS of 32%[7,8]. The CCG-9921 study enrolled 92 patients below three years of age, of whom a third had metastatic disease or residual tumor. The randomized trial consisted of 5 cycles of induction, each lasting 3 weeks and compared regimen A consisting of cisplatin with cyclophosphamide, against regimen B consisting of carboplatin with ifosfamide (with vincristine and etoposide in both arms), and avoidance of irradiation to non-residual, non-metastatic tumor. The 5-year PFS was 32%, with marginal but not statistically significant superiority of regimen A over B, with 83% having avoided irradiation (including four patients with metastatic disease). A subset of these patients (76 out of 92) underwent histological analysis and 22 were found to have the desmoplastic/nodular subtype; within this subtype 18% had metastatic disease and 27% had residual tumor. Of those 18 patients with desmoplastic/nodular subtype and localized disease, 78% remained irradiation-free. Patients with this subtype fared very well, with 5-year PFS of 77%[9,10].

BBSFOP trial, of the French national cooperative group, was conducted from 1990 to 2002 and enrolled 79 patients less than five years of age, with approximately 20% having metastatic disease or residual tumor (Table 2)[11]. The chemotherapy regimen was administered over one year and comprised of two-drug courses administered every 21 days, using carboplatin with procarbazine, followed by etoposide with cisplatin, followed by vincristine with cyclophosphamide, with deferring of irradiation until relapse. The 5-year PFS for all the patients was 29%; for those with residual tumor, this was only six percent and for those with metastatic disease this was 13%, which led to halting of recruitment in these high-risk groups. The 5-year irradiation-free survival was 22% in 64 patients with non-metastatic disease. Neurodevelopmental outcomes were reportedly normal in 48% of 43 evaluable patients; neuropsychological testing was detailed in 33 patients, with those undergoing relapsed therapy regimens (consisting of marrow-ablative chemotherapy followed by irradiation) displaying cognitive impairment[11].

UKCCSG and SIOP collaborative trial, CNS9204, led by the United Kingdom group, spanned from 1993 to 2003 and enrolled 31 patients less than three years of age, with 50% having metastatic or residual disease (Table 2)[16]. The chemotherapy protocol was designed to alternate myelosuppressive drugs with non-myelosuppressive drugs, with either carboplatin or high-dose methotrexate or cyclophosphamide or cisplatin (each with vincristine), every 14 days for one year, with avoidance of irradiation until tumor progression was noted. The 5-year PFS was approximately 35%, with 45% patients avoiding radiation therapy[16].

**Table 2:** Newly diagnosed medulloblastoma regimens without intraventricular methotrexate or high dose chemotherapy

| Trials | Years conducted | Patient # | Age less than | M+ | R+ | VCR | Cytoxan | Cytoxan oral | Ifos | Carbo | Cisp | Etop | Etop oral | CCNU | Vin IV | Cyt | Meth | Pred | HU | Pro | Topo IV | Topo oral | Erlo oral | HD MTX | TMZ oral | Irradiation | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | years | % | % | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | | mg/kg | mg/kg | mg/kg | mg/kg | M0 focal Gy | M0 CSI Gy | M+ focal Gy | M+ CSI Gy |
| Baby POG I (8633) | 1986 to 1990 | 62 | 3 | 42 | 62 | 0.065 | 65 | | | | 4 | 6.5 | | | | | | | | | | | | | | 50 | 24 | 54 | 35.2 |
| Baby POG II (9233) | 1992 to 1998 | 112 | 3 | 24.1 | 60.7 | 0.065 | 65 | | | | 4 to 5 | 6.5 to 7.5 | | | | | | | | | | | | | | 48 to 55.2 | 27 to 34.5 | 48 to 55.2 | 30 to 37.5 |
| CCG-921 | 1986 to 1992 | 111 | 4 | | | 0.05 | 10 | | | | 2 | | | 2.5 to 3.3 | | 10 | 10 | 1.3 | 50 | 2.5 | | | | | | 45 | 23.4 | 59 to 63 | 23.4 |
| CCG-9921 | 1993 to 1997 | 92 | 3 | 34 | 36 | 0.05 | 55 to 65 | | 60 | 10 to 18 | 3.5 | 1.5 to 2.5 | | | | | | | | | | | | | | 50.4 | | 50.4 | 18 to 30.6 |
| BBSFOP | 1990 to 2002 | 79 | 3 to 5 | 19 | 22 | 0.05 | 50 | | | 15 | 1 | 5 | | | | | | | | 4 | | | | | | | | | |
| UKCCSG CNS 9204 | 1993 to 2003 | 31 | 3 | 48 | 54 | 0.05 | 50 | | | 20 | 1.3 | | | | | | | | | | | | | 250 | | 45 to 50 | 25 | | |
| COG P9934 | 2000 to 2006 | 74 | 3 | 0 | 31 | 0.065 | 65 | | | | 3.5 | | 1.7 | | | | | | | | | | | | | 50.4 or 54 | | | |
| SJYC07 | 2007 to 2017 | 81 | 3 | 32 | 16 | 0.03 | 20-50 | 1 | | AUC 5 | 2.5 | 3.3 | | | 0.03 | | | | | | AUC 140 | 0.03 | 3 | 83-167 | | | | 54 | 23.4 to 39.6 |

M+: any metastatic disease, R+: any residual tumor, VCR: Vincristine, Cytoxan: Cyclophosphamide, Ifos: Ifosfamide, Carbo: Carboplatin, Cisp: Cisplatin, Etop: Etoposide, CCNU: Lomustine, Vin: Vinblastine, Cyt: Cytarabine, Meth: Methylprednisolone, Pred: Prednisone, HU: Hydroxyurea, Pro: Procarbazine, Topo: Topotecan, Erlo: Erlotinib, HD MTX: high dose Methotrexate, TMZ: Temozolomide, CSI: Cranio Spinal Irradiation, Gy: Gray

The German cooperative group, HIT-SKK, clinical trials spanned from 1987 to 2005[12-14]. The HIT-SKK'87 protocol enrolled 29 patients less than three years of age with 10% having metastatic disease and 30% with residual tumor (Table 3). For patients with high-risk disease (subtotal resection or metastatic disease) or aged 2.5 to three years at diagnosis, the chemotherapy regimen was designed to include two cycles of induction chemotherapy consisting of procarbazine followed in two weeks by ifosfamide and etoposide followed thereafter in 1.5 weeks by high-dose methotrexate (two doses, each two weeks apart), followed by cisplatin and cytosine arabinoside. The maintenance regimen (57 days per cycle) included procarbazine followed by high-dose methotrexate (three doses given two weekly), followed by vincristine (five weekly doses) and was repeated until irradiation was administered either at three years of age, or immediately for progressive or recurrent tumor. Irradiation for children of three years of age and older consisted of 55.2 Gy to the posterior fossa and 35.2 Gy to the cranio-spinal axis; this was reduced to 24 Gy for younger children with tumor recurrence. For patients with low-risk disease (no residual tumor, no macroscopic disease), the chemotherapy regimen consisted of the maintenance regimen to be given until age three years, when irradiation was administered or until progression was noted. The 10-year PFS was 85% for those with desmoplastic /nodular subtype, 55% for those with incomplete resection, but no survivors were noted with metastatic disease[13].

HIT-SKK'92 protocol was designed on the backbone of the '87 protocol, with the aim to mitigate the dismal neuropsychological outcome of craniospinal irradiation, by replacing it with intraventricular methotrexate for very young children. The study enrolled 43 patients less than three years of age with 28% having metastatic disease and 32% with residual tumor. The chemotherapy regimen spanned six months, and included three cycles of induction, each cycle consisting of one course of cyclophosphamide with vincristine and intra-ventricular methotrexate followed by two courses of high-dose methotrexate with vincristine and intra-ventricular methotrexate, followed by one course of carboplatin with etoposide and intra-ventricular methotrexate, followed by intra-ventricular methotrexate (36 total doses), with irradiation reserved only for children with residual disease. With this strategy, 65% of the 31 patients without metastatic disease avoided irradiation. The 5-year PFS was 50% for patients with residual tumor and 33% for those with metastatic disease. In comparison with the HIT-SKK'87 regimen, the 10-year PFS had improved to 89% for those with desmoplastic/nodular subtype, although it remained unchanged for those with residual tumor (50%); however, there was a definite survival advantage noted for patients with metastatic disease of 33% at 8 years follow-up. In 83% of 23 evaluable patients, asymptomatic leukoencephalopathy was noted, most pronounced at one year off therapy, and correlated with cumulative dosing of intra-ventricular methotrexate. The neuropsychological outcome was evaluated in both studies, with formal testing administered to 32% of patients. The IQ scores were noted to be highest in the healthy controls, then progressively declined from the

systemic chemotherapy group to the combined systemic and intra-ventricular methotrexate group, to the radiotherapy after systemic and intra-ventricular methotrexate group[12].

HIT-SKK'00 protocol was activated for patients with non-metastatic disease, in order to validate the encouraging results from the '92 study. The study enrolled 48 patients less than four years of age, with 31% having residual tumor. The chemotherapy regimen was identical with the '92 protocol, with the addition of two cycles of cyclophosphamide and vincristine alternating with carboplatin and etoposide in patients achieving complete remission. Ninety-seven percent of patients were in complete remission after three cycles. The 5-year PFS for all patients was 57%, for those with large residual tumor was 33%, and for those with desmoplastic / nodular subtype of tumor was 95%. Fifty-nine percent of patients achieved a 5-year irradiation-free survival. Post study modifications included adding focal irradiation for those with non-desmoplastic /nodular histology[14].

**Table 3:** Newly diagnosed medulloblastoma HIT-SKK regimens

| Trial | Years conducted | Patient # | Age Less than | M+ | R+ | VCR | Cytoxan | Ifos | Carbo | Cisp | Etop | Cyt | Pro | HD MTX | IO MTX | Irradiation | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | years | % | % | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | | M0 focal Gy | M0 CSI Gy | M+ focal Gy | M+ CSI Gy |
| HIT-SKK'87 | 1987 to 1993 | 29 | 3 | 10 | 31 | 0.05 | | 100 | | 1.3 | 5 | 13.3 | 3.3 | 167 | | | | 55.2 | 35.2 |
| HIT-SKK'92 | 1992 to 1997 | 43 | 3 | 28 | 32 | 0.05 | 26.6 | | 6.6 | | 5 | | | 167 | 2 | | | | |
| HIT-SKK'00 | 2001 to 2005 | 48 | 4 | 0 | 31 | 0.05 | 26.6 | | 6.6 | | 5 | | | 167 | 2 | | | | |

M+: any metastatic disease, R+ : any residual tumor, VCR: Vincristine, Cytoxan: Cyclophosphamide, Ifos: Ifosfamide, Carbo: Carboplatin, Cisp: Cisplatin, Etop: Etoposide, Cyt: Cytarabine, Pro: Procarbazine, HD MTX: high dose Methotrexate, IO MTX: Intra Ommaya Methotrexate, CSI: craniopsinal, Gy: Gray

"Head Start" trials spanned from 1991 until the present time and introduced dose-intense induction phase chemotherapy followed by a high-dose consolidation phase chemotherapy using marrow-ablative chemotherapy with AuHPCR, in order to avoid irradiation and strengthen response rate (Table 4)[18-21]. The "Head Start" I trial enrolled 13 patients, with 12 being less than three years of age, with 15% having metastatic disease and 54% having residual tumor. The chemotherapy regimen involved five cycles of induction chemotherapy, utilizing cisplatin and vincristine (day one), followed by cyclophosphamide (days two and three) and etoposide (days two, three and four). Bone marrow harvesting was performed prior to the third cycle. Patients proceeded to a single cycle of consolidation chemotherapy if residual tumor had regressed or was resected with second-look surgery or was at least stable. The consolidation regimen involved three consecutive days of marrow-ablative chemotherapy including carboplatin (dosing based on area under curve), followed by three days of thiotepa and etoposide, followed by AuHPCR. Response to induction chemotherapy was noted in 85% patients; two toxic deaths were noted, and 85% patients proceeded to the consolidation phase. None of the patients developed leukoencephalopathy. The 2-year PFS was 38% for all patients, and the 5-year PFS was 29% for patients with non-

metastatic disease with residual tumor. The neuropsychological outcomes were evaluated in seven survivors; all tested parameters were average to low-average for various domains[18,20,28].

"Head Start" II study enrolled nine patients with medulloblastoma under age three years with non-metastatic disease, 11% with residual tumor and 21 patients under age 10 years at a median age of 3.2 years with metastatic disease and 38% with residual tumor. The chemotherapy protocol was intensified and compressed compared to "Head Start" I and comprised of the induction regimen with five cycles, with each cycle lasting at least 21 days and consisting of vincristine, cisplatin, cyclophosphamide and etoposide, as in "Head Start" I, followed - for patients with metastatic disease - by HD-MTX on day four. The consolidation regimen was identical with the "Head Start" I protocol. The analysis of nine patients (all with non-metastatic disease) has been published in conjunction with 12 patients treated on the "Head Start" I protocol[20]. Thus, a pooled analysis of 21 patients under three years of age with non-metastatic disease was reported, with 62% showing complete response to induction, a 5-year PFS for all patients reported as 52%, and for those with desmoplastic /nodular subtype (9 out of 21 patients) reported as 67%. Of the nine patients enrolled on the "Head Start" II protocol, none developed leukoencephalopathy, and one patient suffered from toxic death in the post-consolidation phase. For the 21 patients (all with metastatic disease), complete response to induction therapy was seen in 81% of patients. with 100% patients proceeding to consolidation phase. Irradiation-free survival was noted in 55% of 11 patients. The 3-year PFS was 49%. This protocol led to organ toxicities, needing hospitalizations, such as gastrointestinal and infectious complications[19]. Neuropsychological outcomes for surviving children enrolled on "Head Start" II revealed preservation of functioning compared with baseline, even in those who received high-dose methotrexate[29].

"Head Start" III study enrolled 92 patients, with 55% having metastatic disease and 46% with residual tumor. The study enrolled all medulloblastoma patients under six years of age at diagnosis and patients between six and 10 years of age with high-risk (metastatic or localized residual) disease. The induction chemotherapy regimen comprised of either three or five cycles, with cycles one, three and five similar to the "Head Start" II induction regimen and cycles two and four consisting of cyclophosphamide, vincristine, oral etoposide and oral temozolomide. Due to emerging toxic deaths in patients below 18 months of age, the induction regimen was subsequently modified to a lower dose of methotrexate and to a modestly lower dose of cyclophosphamide. Patients in remission proceeded to a single consolidation cycle identical with the "Head Start" I and II protocols. Of the 92 patients on study, 50% showed complete response to the induction regimen, and 74% of patients proceeded to the consolidation phase. Seven patients died of chemotherapy-related toxicity. The 5-year PFS was 46% for all patients and 35% for patients with metastatic disease. Patients with desmoplastic /nodular medulloblastoma had 89% 5-year PFS and 78% irradiation-free PFS. Due to the modifications to the induction regimen, the

organ toxicities were subsequently significantly reduced. Close to five years from the end of therapy, 26% of patients completed the neurocognitive testing, with IQ and memory evaluation displaying average scores and processing speed and adaptive functioning showing low average scores[21,30].

"Head Start" 4 study opened in 2015 and has recently completed enrollments for all the patients. The induction chemotherapy regimen was identical with "Head Start" II, with all patients receiving high-dose methotrexate in all cycles, either three or five cycles depending upon completeness of response. Low-risk patients (defined as SHH or Wnt medulloblastoma) underwent a single cycle of consolidation identical with the "Head Start" I, II and III regimens. High-risk patients (non-SHH/non-Wnt) were randomly assigned to either one cycle or three tandem cycles of consolidation chemotherapy. If less than a complete remission to induction was achieved after three cycles, the patients receive two additional induction chemotherapy cycles (without vincristine) followed by the consolidation phase. The induction chemotherapy was designed to be both dose-intense and dose-compressed (21 days' course). The consolidation three-cycle tandem regimen was based upon the CCG-99703 phase I /II trial (see below), utilizing two consecutive days of high-dose carboplatin (dosing based on area under curve) and thiotepa, followed by AuHPCR. Radiation therapy was reserved for those patients aged six years and older, and for those younger than six years of age if complete remission was not achieved. Neuropsychological outcomes are being monitored long-term on all patients.

The Australian/New Zealand Children's Hematology Oncology Group trial, ANZCCSG BabyBrain99, was conducted from 1999 to 2005 and accrued nine children with medulloblastoma less than four years of age, with no information available on the percentage of high-risk disease (Table 4)[31]. The chemotherapy protocol consisted of induction with two courses of cisplatin and oral etoposide, given every 21 days, followed by course three with vincristine and etoposide and three days of cyclophosphamide, followed by course four with vincristine and etoposide (higher dose) and three days of cyclophosphamide (higher dose). Patients with no evidence of tumor went on to a consolidation regimen consisting of carboplatin given over four days followed by melphalan then AuHPCR. Focal radiation therapy was given to patients older than two years of age in remission. Toxic deaths were noted. The 5-year PFS was 33% in all tumor types (including medulloblastoma) and 22% in patients with residual tumor (including medulloblastoma). Ototoxicity was monitored and not found to be significant. Neuropsychological evaluations were done on a small number of patients, hence could not be reported[31].

Table 4: Newly diagnosed medulloblastoma regimens using high dose chemotherapy

| Trial | Years conducted | Pt # | Age Less than | M+ | R+ | AuHPCR | single/tandem transplant | Induction | | | | | | | | | | | Consolidation | | | | | | | Irradiation | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | VCR | Cytoxan | Cytoxan oral | Cisp | Etop | Etop oral | Vin | Topo oral | Erlo oral | HDMTX | TMZ oral | VCR | Thio | Carbo | Etop | Cytoxan | Mel | Topo | M0 focal | M0 CSI | M+ focal | M+ CSI |
| | | | years | % | % | % | # | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | mg/kg | Gy | Gy | Gy | Gy |
| **HeadStart I** | 1991 to 1995 | 13 | 6 | 15 | 54 | 85 | 1 | 0.05 | 65 | | 3.5 | 4 | | | | | | | | 10 | 17 | 8.3 | | | | | | | |
| **Head Start II** | 1997 to 2003 | 30 | 10 | 70 | 27 | 100 | 1 | 0.05 | 65 | | 3.5 | 4 | | | | | 400 | | | 10 | 17 | 8.3 | | | | | | | 23.4 |
| **Head Start III** | 2003 to 2009 | 92 | 10 | 55 | 46 | 74 | 1 to 3 | 0.05 | 55 to 65 | | 3.5 | 4 | 1.7 | | | | 270 to 400 | 6.5 | | 10 | 17 | 8.3 | | | | 55.8 | 23.4 | 55.8 | 18 to 36 |
| **Head Start IV*** | 2015 till date | unk | 10 | unk | unk | unk | 1 to 3 | 0.05 | 65 | | 3.5 | 4 | | | | | 400 | | | 10 | 17 | 8.3 | | | | 23.4 | 50.4 to 54 | 18 to 23.4 | 50.4 to 55.8 |
| **ANZCCG BabyBrain99** | 1999 to 2005 | 9 | 4 | unk | unk | unk | 1 | 0.05 | 40 | | 4 | 2 to 7.5 | | | | | | | 0.05 | | 3 mg/ml/min | 15 | 70 | 4.6 | | 50.4 | | 54 | |
| **CCG-99703** | 1998 to 2004 | 36 | 3 | 28 | 36 | unk | 3 | 0.05 | 60 | | 3.5 | 2.5 | | | | | | | | 10 | 17 | | | | | | | | |
| **ACNS0334** | 2007 to 2016 | 46 | 3 | unk | unk | unk | 3 | 0.05 | 60 | | 3.5 | 2.5 | | | | | 400 | | | 10 | 17 | | | | | | | | |

*ongoing study

M+: any metastatic disease, R+: any residual tumor, AuHPCR: patients moving to Autologous HematoPoetic Cell Rescue, VCR: Vincristine, Cytoxan: Cyclophosphamide, Cisp: Cisplatin, Etop: Etoposide, Vin: Vinblastine, Topo: Topotecan, Erlo: Erlotinib, HD MTX: high dose Methotrexate, TMZ: Temozolomide, Thio: Thiotepa, Carbo: Carboplatin, Mel: Melphalan, AUC: Area Under Curve, CSI: Cranio Spinal Irradiation, Gy: Gray

CCG-99703 study was a phase I /II trial, conducted from 1998 to 2004, and enrolled 36 patients less than three years of age, of whom 28% had metastatic disease and 36% had residual tumor (Table 4)[22]. The phase I study objective was to determine the maximum tolerated dose of thiotepa. The phase II study protocol involved an induction chemotherapy regimen with three cycles similar to "Head Start" I (i.e., without methotrexate). Those patients following induction chemotherapy, with no evidence of tumor progression, proceeded to consolidation chemotherapy, consisting of three sequential cycles of two consecutive days of marrow-ablative carboplatin and thiotepa, followed by AuHPCR. There was a 2.6% toxic death rate from the consolidation chemotherapy. Forty four percent patients achieved complete response to induction chemotherapy. The 5-year PFS was 60% for all patients, 29% for those with residual tumor, 30% for those with metastatic disease and 79% for those with desmoplastic/nodular medulloblastoma. The 5-year irradiation-free survival was 48% for 23 patients[22].

COG ACNS0334 phase III randomized study was opened in 2007, and closed to accrual in 2016, enrolled 46 patients less than three years of age, excluded localized residual and non-metastatic medulloblastoma (Table 4)[23]. The chemotherapy protocol was designed to study if the addition of high-dose methotrexate to the backbone of the CCG-99703 induction regimen would improve the complete remission rate. Radiation therapy was not part of the protocol. The induction regimen consisted of three cycles given at least 21 days apart, each cycle consisting of vincristine, three days of etoposide and two days of cyclophosphamide, followed by cisplatin. For patients randomized to receive high-dose methotrexate, this was given at the beginning of each induction cycle, along with vincristine and only when methotrexate clearance was achieved, the three days of etoposide and two days of cyclophosphamide followed by cisplatin were administered. The consolidation regimen consisted of three cycles, each cycle spanning over at least 21 days and comprising of two days of carboplatin and thiotepa. The 5-year OS was 100% for children with the SHH subtype (all metastatic, with or without methotrexate). The 5-year OS was 80% for group 3 subtype with the addition of methotrexate but only 40% for the group 3 subtype without methotrexate. The 5-year irradiation-free survival rate was 57%. Toxic deaths related to chemotherapy were 4%[23].

The St. Jude trials spanned from 2007 until the present time (Table 2)[27], and were devised to improve survival for patients using risk-adapted therapy and to understand the implication of methylation profiling on prognosis. For St. Jude study purposes, the low-risk cohort included patients less than three years of age, without metastatic disease and with less than 1 $cm^2$ residual tumor and desmoplastic /nodular medulloblastoma; the intermediate-risk cohort consisted of patients under three years of age, without metastatic disease and less than 1 $cm^2$ residual tumor and subtype other than desmoplastic /nodular, *or* those with desmoplastic /nodular subtype with residual tumor, *or* three to five year old patients without metastatic disease or residual tumor without MYC or MYCN amplification; the high-risk cohort included all patients less than three years of age with

metastatic disease. The SJYC07 study enrolled 81 patients under three years of age, with 32% having metastatic disease and 16% having residual tumor. The induction chemotherapy regimen consisted of four cycles, with each cycle lasting 28 days, and comprising of high-dose methotrexate followed by vincristine and cisplatin followed by cyclophosphamide followed (for high-risk patients only) by five doses of vinblastine given on alternate days. The consolidation regimen was stratified by risk cohorts, with low-risk cohort assigned to receive two cycles of carboplatin, cyclophosphamide, and etoposide; the intermediate-risk cohort received focal irradiation if older than one year or received low-risk group maintenance therapy while awaiting focal irradiation once they turned one year old; the high-risk cohort was assigned to receive topotecan and cyclophosphamide *or* craniospinal irradiation if older than three years. Post-consolidation, all patients were assigned to receive oral maintenance chemotherapy for six months, consisting of cyclophosphamide, topotecan and erlotinib. The 5-year PFS for the low-risk cohort was 55%, for the intermediate-risk cohort was 25% and for the high-risk cohort was 17%. No toxic deaths were reported. Methylation profiling revealed that the iSHH-II sub-group had an excellent outcome to low-risk chemotherapy, statistically superior to those in the iSHH-I subgroup; however, still lower than wither "Head Start" or HIT-SKK protocols. This study suggested that the design of future trials be based on molecular subgroups[27].

SJiMB21 study opened in 2022 and began enrolling patients less than five years of age. The chemotherapy protocol is designed as a risk-stratified approach based on molecular groups, with SHH and Group 3 (with Group 4) treatment arms. The SHH group is subdivided into SHH-2 and SHH-1 (with SHH-3) subgroups. The SHH-2 arm includes patients less than three years of age, and patients three to five years of age without metastatic disease, assigned to receive low-intensity systemic chemotherapy. The SHH-1 arm (with SHH-3) includes patients less than three years of age, assigned to receive high-dose methotrexate with systemic chemotherapy. The Group 3 arm (with Group 4) includes patients assigned to systemic chemotherapy until three years of age, followed by risk-adjusted craniospinal irradiation. Accrual is currently ongoing.

## Discussion:

This comprehensive review of prospective clinical trials for newly diagnosed young children with medulloblastoma provides a comprehensive analysis of the evolution of multi-agent chemotherapy protocols that have been designed empirically to improve the progression-free and irradiation-free survival for these young children.

It has been extremely challenging to design chemotherapeutic regimens with curative intent, but several multi-disciplinary and multi-national collaborative groups have been able to introduce highly potent chemotherapy agents and formulate the use of intravenous, oral and intraventricular approaches to deliver chemotherapy, in order to reach this goal. The use of agents such as cisplatin, high-dose cyclophosphamide, high-dose methotrexate and the design of dose-intense and compressed induction regimens along with the introduction of high-dose, marrow-ablative chemotherapy with autologous

hematopoietic progenitor cell rescue (initially bone marrow-derived, and now almost exclusively peripheral blood derived) has dramatically improved complete remission rates, especially for the desmoplastic nodular subtype.

Briefly, the first POG and CCG studies provided the framework for designing chemotherapy-only or irradiation-delaying or avoiding protocols; this approach generated progression-free survivals approaching 20 to 30%. The HIT-SKK studies were revolutionary in their introduction of high-dose intravenous methotrexate and of intraventricular methotrexate (in lieu of irradiation), which catapulted the progression-free survival for those with the desmoplastic /nodular subtype to about 90%, although the classic /large cell anaplastic subtypes continued to show poor progression-free survival of approximately 30%. The "Head Start" studies successfully integrated dose-intense induction chemotherapy (including high-dose intravenous methotrexate for all patients from "Head Start" III onwards) with a high-dose marrow-ablative consolidation regimen into the treatment protocols, and have evolved to provide less-intense therapy for the desmoplastic /nodular subtype, leading to a significant improvement in progression-free and irradiation-free survivals to approximately 90% for those with the desmoplastic /nodular subtype, but with the classic and large cell anaplastic subtypes still faring less well, with progression-free survival of approximately 40 to 50%. The St. Jude studies have designed trials with a risk-stratified approach and have been at the forefront of incorporating molecular sub-classification to redefine risk-groups within their study cohorts.

The overarching conclusion from this review of chemotherapy is that regimens using either systemic high-dose methotrexate and intra-ventricular methotrexate and /or marrow-ablative consolidation chemotherapy have made the largest impact in significantly improving the survival for patients with the desmoplastic/nodular subtype of medulloblastoma, despite the young age and high-risk disease status. These regimens have also generated superior progression-free, irradiation-free and overall survivals compared with those not including either high-dose systemic and intraventricular methotrexate or marrow-ablative consolidation therapies, although these improvements have been modest, and leave much room for improvement.

Studies reviewed here have succinctly highlighted the toxicities from various chemotherapy agents, namely leukoencephalopathy from the use of intraventricular methotrexate and multi-organ dysfunction from the use of dose-intense and compressed chemotherapy regimens. Several studies have made the difficult effort to integrate quality of life evaluation and neuropsychological testing into their protocols; of these, the HIT-SKK series and the "Head Start" series have been the leaders in providing meaningful analyses on how their studies have preserved or stabilized the IQ scores through irradiation-avoiding approaches for these young children.

The strong commitment, to avoid or at least delay cranial irradiation for the youngest children with medulloblastoma, has risen from the well-studied short-term and irreversible long-term toxicities from such irradiation;

however, most trials have recognized that delaying (instead of denying) irradiation does not mitigate the effects of such irradiation. Although we did not expound on therapies for relapsed or progressive medulloblastoma in this review, irradiation remains the mainstay to prolong survival time for such patients.

## Conclusion:

As medulloblastoma is well known to be a heterogenous tumor (with four major molecular sub-groups of Wnt, SHH, Group 3 and Group 4, each with their own further sub-groups), targeting of the genetic pathway, epigenetic machinery and tumor microenvironment is being studied in clinical trials, in order to improve the survival rate for refractory, relapsed or recurrent medulloblastoma[32,33]. Based on the success of such trials, systematic incorporation of novel agents into standard of care therapy for newly-diagnosed, high-risk clinical cohorts and specific molecular sub-groups will be pertinent to achieve long-term remission for young children[34]. For example, therapies targeting the epigenetic machinery are in trial, such as the histone deacetylase inhibitors vorinostat and fimepinostat and the EZH2 inhibitor tazemetostat[35, 36]. Future trials using PRMT5 inhibitors, such as TNG908, are being designed for the highly aggressive subtype of MYC-driven medulloblastoma.[37] In the meantime, we await outcomes from the "Head Start" 4 randomized trial for outcomes of high-risk (non-Wnt, non-SHH) medulloblastoma to determine which if any sub-groups benefit from tandem rather than single cycle marrow-ablative consolidation chemotherapy, as well as from the current St. Jude infant trial (SJiMB21), incorporating both intra-ventricular chemotherapy as well as a targeted biological agent, for the high-risk patients.

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