Desmoplastic Nodular Medulloblastoma in Young Children: A Management Dilemma

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Abstract:

Background:

Children with desmoplastic nodular medulloblastoma (DNMB) have excellent survival, leading multiple groups globally to attempt reduction of treatment-related morbidity. In 2013, the Children’s Oncology Group began a clinical trial (ACNS1221) eliminating both radiation therapy (RT) and intraventricular methotrexate for children under 3 years of age with localized DNMB, aiming to build upon the excellent outcomes of the German (HIT) trials. ACNS1221 has recently closed due to increased incidence of recurrences noted at the 2-year interim analysis, raising important questions regarding optimal therapy for DNMB.

Methods:

A review of major clinical trials that included children with DNMB was performed through July 2017.

Results:

One hundred and eighty eight DNMB patients enrolled on 11 prospective clinical trials were identified. The use of marrow-ablative chemotherapy and autologous hematopoietic cell rescue (AuHCR), or treatment with intraventricular methotrexate has been associated with excellent outcomes. RT was usually required for patients with evidence of disease at the end of therapy.

Conclusions:

The minimal intensity and duration of chemotherapy required to maximally cure children with DNMB without need of RT, remains unknown. Further trials are required to better identify a subset of DNMB patients who can be cured without marrow-ablative chemotherapy or intraventricular methotrexate.
Keywords:
Medulloblastoma; desmoplastic nodular; ACNS1221; HIT-SKK; chemotherapy.

Importance of the Study:

Multiple questions have been raised around the globe on the best way to manage children less than three years of age with localized non-metastatic desmoplastic nodular medulloblastoma (DNMB) since the early closure of the Children’s Oncology Group clinical trial (ACNS1221) and the St. Jude prospective clinical trial SJYC07. Hence, a comprehensive review of the literature for all major prospective clinical trials that included DNMB patients was warranted. This review details the current treatment options and provides some clues regarding the best route to move forward, which may help guide the design of future prospective clinical trials specific for children with localized DNMB.

Introduction:

Medulloblastoma (MB) is the most common malignant brain tumor in children less than 4 years of age. According to the 2007 WHO classification, MB was divided based on histology into 4 subtypes: desmoplastic/nodular medulloblastoma (DNMB), classic MB, MB with extensive nodularity (MBEN), large cell and anaplastic MB [(Supplementary Figures 1 and 2) and (Supplementary Table 1)]. The recent advances in molecular biology have led to the recognition of the genetic landscape of MB, which has been incorporated in the latest edition (2016) of the CNS WHO classification. The previous histological classification is still included, but a genetically-defined subgrouping has additionally been integrated; Wingless (WNT)-activated, Sonic hedgehog (SHH)-activated and TP53-mutant, SHH-activated and TP53-wildtype, and lastly non-WNT/non-SHH Groups 3 and 4.
DNMB occurs in approximately 44% (range 32-61%) of infants under 3 years of age diagnosed with MB. The incidence decreases to 10-20% in children 3-5 years of age. The SHH subgroup is very common in children < 5 years of age; while virtually all DNMB are SHH, not all SHH are DNMB.

Radiotherapy (RT) is a highly effective modality in the treatment of MB but causes a number of significant and irreversible side-effects in young children with brain tumors, including central endocrinopathies, vasculopathies, RT-induced second malignancies and severe cognitive damage in a dose-, volume- and age-related manner. For many young patients treated with cranial RT, and even some older ones, survivors commonly cannot live independently, gain meaningful employment or get married.

Several clinical trials have attempted to either reduce the RT dose and/or field or avoid RT entirely for young children diagnosed with MB, in order to minimize or avoid the detrimental long term side-effects of RT on the growing brain. An analysis of these trials have demonstrated that DNMB has excellent overall survival rate despite dose reductions or even avoidance of RT when compared to the other three MB histological subtypes. Rutkowski et al showed that the rates for 8-year event free survival (EFS) and overall survival (OS) were 86% and 95% respectively in 21 children with MBEN, and 48% and 72% respectively in 87 children with DNMB in a meta-analysis that pooled data from 5 groups (France, Italy, USA, UK and Germany).

The German HIT-SKK protocols (87, 92 and 2000) used a chemotherapy strategy that spared RT, and replaced it mainly with intravenous and intraventricular methotrexate (MTX), except for those patients with residual or metastatic disease. The Germans reported an excellent 8-year progression free survival (PFS) of 78 +/-4% when their longer term data for their expanded cohort of patients (115 patients) treated according to the HIT protocols (SKK’87, SKK’92, HIT 2000 and HIT Registry) were presented at
the International Symposium on Pediatric Neuro-Oncology (ISPNO) in 2016. Despite the great OS, concerns were raised regarding the occurrence of leukoencephalopathy as well as poor neurocognitive outcomes of those treated with intraventricular MTX.

The success of the German RT-sparing strategy led the Children’s Oncology Group (COG) to design a clinical trial (ACNS1221) specifically for children with DNMB (ClinicalTrials.gov: NCT02017964). ACNS1221 modified the German HIT-SKK’2000 treatment protocol, eliminating intraventricular MTX for patients less than 4 years of age with M0 DNMB and MBEN. Unfortunately, ACNS1221 closed in August 2016 when an interim analysis showed that the 2-year PFS was lower than the 90% PFS required by the study. This unexpected closure has generated discussions on how to best treat non-metastatic, completely resected (R0M0) DNMB patients.

Methods:

We have reviewed the English literature for major prospective clinical trials that included details on number of DNMB patients and their outcomes [Table 1]. The authors searched PubMed through July 2017. Search items included the words medulloblastoma AND desmoplastic AND nodular. Eleven major clinical trials from North America and Europe were included. The details of therapy used on each of these trials along with their outcomes are described in Table 1. We have also included preliminary results of a few prospective clinical trials that were presented at international meetings and were published in peer-reviewed medical journals.

Results:

Historically, clinical trials for children with MB have been designed to defer RT until patients were older than 3 years of age or until progression; these included the German HIT-SKK’87 trial which was designed for patients less than 3 years of age with MB. As expected when RT was used in children less than 3
years of age, neuropsychological tests performed at a median of 6.1 years from diagnosis demonstrated mean IQ scores that were significantly lower compared with healthy controls within the same age group.\textsuperscript{17}

HIT-SKK’92 intended to avoid the significant morbidity associated with the use of RT in young children by administering intraventricular MTX through a subcutaneous reservoir along with high-dose intravenous MTX.\textsuperscript{18} Intraventricular MTX was used instead of RT in patients with complete remission (CR) at the end of chemotherapy, while those with less than a CR did receive RT when they reached 18 months of age. The neurocognitive outcomes of 14 MB patients who received systemic and intraventricular chemotherapy without RT were significantly better than those who had received RT and systemic chemotherapy. Desmoplastic histology was identified as a favorable prognostic factor on multivariate analysis, while the presence of macroscopic metastatic disease and children less than two years of age were found to have a higher risk of relapse or death.

Rutkowski \textit{et al} published in 2009\textsuperscript{17} a comparison between both the HIT-SKK’87 and ‘92 studies. They showed no differences in the 10-year PFS and OS for those patients with DNMB and MBEN treated on both trials, and concluded that eliminating RT for these two subtypes did not affect the survival. Interestingly, on further multivariate analysis for all the patients on both trials, treatment with HIT-SKK’87 had a higher risk of recurrence when compared to those treated with HIT-SKK’92. Likewise, the intelligence co-efficient (IQ) scores for the patients treated on HIT-SKK’87 were inferior when compared to non-irradiated children on HIT-SKK’92.

The results from the above-mentioned trials paved the way for the development of the HIT-SKK’2000 trial\textsuperscript{19}, which increased the age of enrollment from 3 to 4 years and the number of cycles to five instead of three in order to further improve the outcomes and limit RT use. Excellent PFS and OS were observed
for the 19 patients with DNMB (13) and MBEN (6). One patient with DNMB relapsed locally at 1.7 years of age and was successfully salvaged with craniospinal RT and systemic chemotherapy, and was still alive at 4.1 years following completion of therapy.

While 50% of MB patients were successfully salvaged in HIT-SKK’92, only 10% were salvaged in HIT-SKK’87. The salvage outcomes for DNMB patients treated on all HIT trials as well as the HIT registry were presented at ISPNO in 2016. The authors analyzed data from 115 patients with DNMB and MBEN and described 29 patients (25 DNMB and 4 MBEN) who failed a primary HIT strategy. Excellent outcomes were reported, with an 8-year OS of 91 +/- 3% and PFS of 78 +/- 4%. On further analysis, the independent risk factors for progression were age more than 3 years and the presence of metastatic disease. These patients were salvaged using a combination of surgery, chemotherapy, high-dose chemotherapy as well as RT, with a very decent 5-year OS after failure of 64 +/- 10%. The rate of salvage therapy for these patients on the HIT trial was similar to that of the patients treated with chemotherapy only on the French SFOP prospective clinical trial, where salvage therapy included RT and high-dose chemotherapy with busulfan and thiotepa, and the 3-year OS after local relapse or progression was 61%.

Parallel to the HIT-SKK studies, the Children’s Cancer Group (CCG), which later combined with the Pediatric Oncology Group (POG) to become the COG, attempted to reduce the long term side effects of RT on the growing brain in young patients with MB by conducting a chemotherapy-only trial (CCG-9921) for children <3 years with malignant brain tumors, including high risk MB. Therapy consisted of surgery followed by randomization to one of two chemotherapy regimens and RT. Infants younger than 1.5 years of age were not randomized and were assigned to receive 8-in-1 chemotherapy and delayed RT. RT was used for four out of the 18 patients with localized disease, only one was alive at the time of publication. On the other hand, all four patients with metastatic disease were alive at the last contact; only two had received RT. There were no significant differences in the response rates between either of
the two induction regimens; however, regimen A was considered less toxic. CCG-9921 demonstrated that chemotherapy-only strategies can be effective for patients with DNMB, even for a subset of patients with metastatic disease, without the need for RT or even high dose chemotherapy with autologous hematopoietic cell rescue (AuHCR).

CCG-99703\textsuperscript{26} (Phase I dose escalation) was designed based on the promising results of the Head Start I regimen (discussed below). It is worth noting that only one out of the enrolled 14 patients received RT, and the only patient with M1+ disease experienced recurrent disease. The outcomes for CCG-9921 (15 months treatment duration) were compared with CCG-99703 (6 months treatment duration) and there was no difference noted in the EFS for DNMB (77 +/- 9% versus 78.6 +/- 11%)\textsuperscript{26}. This raised the possibility that intensive marrow-ablative high dose chemotherapy with AuHCR may not be needed for the DNMB subgroup of MB, especially those with R0M0 disease.

The POG study P9934 used conformal RT to the posterior fossa to all the patients along with induction and maintenance chemotherapy. Nevertheless, the 39 infants (8 months - 3 years) with non-metastatic DNMB had poor OS and EFS\textsuperscript{27}. Similarly, the outcomes for 20 patients with DNMB treated on POG 9233/34 (Baby POG-2) were even worse despite intensifying the chemotherapy doses\textsuperscript{27,28}.

The POG and the French Society of Paediatric Oncology (SFOP) also led two prospective clinical trials [POG 8633/34 (Baby POG 1)\textsuperscript{22,23} & Baby Brain French Society of Paediatric Oncology (BBSFOP)\textsuperscript{15}] aiming to reduce the long-term side effects of RT by either cutting down the dose of RT or completely eliminating it, but no data were provided to distinguish the outcomes according to MB histological subtypes, and therefore we did not include either studies in our analysis.

The Head start (HS) studies used induction chemotherapy followed by consolidation with marrow-ablative chemotherapy and AuHCR in the management of infants with malignant brain tumors,
specifically MB. The main difference between Head Start (HS) I and II\textsuperscript{16,29} was that patients with disseminated MB on HS II received high-dose MTX. Both trials showed a decent outcome for the limited cohort of DNMB patients but there were three toxic deaths noted on HS I while only one toxic death was noted on HS II amongst the DNMB patients.

The HS III protocol attempted to reduce the number of cycles with cisplatin and high-dose MTX for patients with metastatic disease, with cycles two and four being substituted with temozolomide, oral etoposide, cyclophosphamide and vincristine. However, all patients with localized or metastatic disease received this regimen, so high-dose MTX was included in the regimen for the first time for patients with localized disease. Only one out of 15 patients with M0 DNMB died from CNS hemorrhage related to an accidental fall, while the remaining 14 patients are surviving without receiving RT. The improvement in the EFS and OS on HS III might be attributed to the advances in the supportive care provided to these patients when compared to HS I and II. However, the addition of high-dose MTX to the induction regimen might also have played an important contributing factor in improving the outcomes for these patients. It is worth noting that the 11 DNMB patients with metastatic disease on HS III have had excellent results with a 5-year OS of 82 +/- 12% and EFS of 81 +/- 12%. Two patients with disseminated disease died, one from progressive disease post-AuHCR and one from veno-occlusive disease and multi-organ failure post-AuHCR. Only a third of the surviving patients with M+ disease received CSI\textsuperscript{30}.

The United Kingdom Children’s Cancer Study Group (UKCCSG) and International Society of Paediatric Oncology (SIOP) published the results of their cooperative clinical trial CNS9204\textsuperscript{31} for infants with malignant brain tumors, including MB. There were only three patients with R0M0 DNMB, while there were 6 patients with R1M0 and 8 patients with metastatic disease which might have contributed to the poor EFS for these patients. Interestingly the 3 patients (all DNMB) who received chemotherapy as their
only adjuvant treatment were alive without disease progression at 9.82, 9.96 and 9.97 years (R0M3, R1M0 and R1M0, respectively).

It is worth noting that HIT-SKK protocols and CSN 9204 were the only trials reporting the number of patients of DNMB and MBEN separately, but they grouped them together when analyzing the PFS or the OS. This probably did not affect the analysis of their data, as there are no known differences in the outcomes between DNMB and MBEN. The other prospective clinical trials [Table 1] did not exclude MBEN patients, but included both DNMB and MBEN under “DNMB”.

Upadhyaya has recently presented the St. Jude’s experience with reduced intensity chemotherapy which included an epidermal growth factor inhibitor, erlotinib, during maintenance chemotherapy for children less than 3 years of age with M0 DNMB (SJYC07) at the Society of Neuro-Oncology meeting (SNO)\textsuperscript{32}. Unfortunately, the study was closed early after 23 patients were enrolled, when the observed 1-year PFS fell below the monitoring threshold of 80%. Rapid progression was also noticed (similar to ACNS1221 below); nine patients progressed at a median time of 9.3 months from start of therapy. Also noteworthy is that a significant proportion of patients relapsed with metastatic disease (5 local, 3 distant and 1 combined).

The recently closed COG ACNS1221 trial was designed to build upon the excellent success rate reported by HIT-SKK’2000 protocol. It was the first study performed by the COG to incorporate the DNMB histologic subtype into the clinical risk classification at the time of diagnosis. Patients with non-metastatic DNMB less than 4 years of age were enrolled. The primary objective was to estimate the PFS associated with treatment as per HIT-SKK’2000 without intraventricular MTX, while the endpoint was to look for evidence that the 2-year PFS rate is higher than 90%. The study closed for lack of efficacy when the interim analysis after the first 15 patients had been enrolled and observed for the 2-year outcome.
endpoint. The predicted PFS rate was less than the threshold of acceptance (<74%) and suggested that the trial would not achieve the 90% PFS threshold. Only the preliminary data on type of relapse (focal versus disseminated) is available.

Discussion:

The concept of completely eliminating RT from the treatment regimen of infants with MB was first introduced by Jan van Eys in 1985\textsuperscript{33}, who along with Joann Ater published a follow up analysis in 1997 on twelve patients with MB\textsuperscript{34}. Eight patients were still alive at the time of the publication without any evidence of disease with a median survival of 10.6 years (range, 6.2 to 15.2 yrs). There was no information regarding the MB subtype of these patients, but all of them had received MOPP (mechlorethamine, vincristine (oncovin), procarbazine, and prednisone) chemotherapy and only those who relapsed received RT.

DNMB was identified in multiple studies as a favorable prognostic factor in patients with MB and this has raised the possibility that RT-sparing treatment strategies might maintain the excellent outcomes while reducing treatment related morbidity. A meta-analysis published in 2010 that pooled data of 108 children with DNMB and MBEN from multiple prospective clinical trials demonstrated no significant difference between patients with localized or metastatic DNMB/MBEN in the 8-year EFS (54 ± 5% vs 56 ± 12% respectively)\textsuperscript{5}. Despite the diversity in the treatment regimens included, they were all aiming to avoid or defer RT, and these results indicate that patients with DNMB/MBEN can be treated with an RT-sparing strategy regardless of the presence or absence of metastatic disease.

The incorporation of MTX (intravenous and/or intraventricular) into the treatment protocols appears to play an important role in improving the outcomes, as noted in both the HIT and HS treatment protocols. This was illustrated in the analysis done by Pompe R et al\textsuperscript{35}; the survival of those who had received more
than 75% of the dose of intraventricular MTX was higher compared to the survival of those who received less than 75% of the dose. One of the major issues that emerged with the use of intraventricular MTX on the HIT-SKK'92 was the detection of leukoencephalopathy with MRI changes in 19 of 23 patients, although all changes were reported to be asymptomatic and 10 were transient. As far as the MTX administration and feasibility on HIT-SKK'2000, out of the 211 patients who had an intra-Ommaya reservoir placement, nine experienced acute MTX neurotoxicity and one patient died from toxic oedema followed by seizures. The long term toxic side effects of intraventricular MTX are still under evaluation in the HIT-SKK trials.

The toxic deaths noted on HS III raise questions on whether R0M0 DNMB patients really need this more intensive chemotherapy regimen. The high-dose cyclophosphamide followed by oral temozolomide and etoposide was likely responsible for the marked immunosuppression observed and might be an area were reductions in therapy could be considered. One of the major long term toxic effects of treatment on the HS studies was ototoxicity; 62% of patients (18/29) developed abnormal hearing and 38% required hearing aids. Fortunately, these same patients demonstrated very good long term neurocognitive outcomes and quality of life.

Our review included patients who were treated in prospective clinical trials over more than 30 years. Hence, we have to be careful when analyzing the data from all these studies given the several changes that the pathological classification (morphologic and molecular) of MB has undergone over multiple versions of the CNS WHO classification. This also sheds the light on the importance of evaluating the data from these valuable prospective clinical trials, which might provide an important insight on the differences in the outcome based on the current 2016 CNS WHO integrated molecular and histological classification of MB. It is also imperative to include the RT-free survival in the analysis of future trials; unfortunately this highly valuable data was not included in our analysis since many of the trials did not
include details regarding patients who had not received RT. Of note, the difference noted in EFS and OS for some of the trials, most likely reflecting the success of salvage therapies in patients with DNMB, which usually includes surgery, RT and/or (if not previously used) marrow-ablative chemotherapy with AuHCR, rather than any new 'targeted' agents or conventional chemotherapy.

In spite of the recent closure of ACNS1221, the concept of administering chemotherapy-only strategies as a first-line treatment for patients with DNMB is still appealing. However several factors have to be taken into consideration before designing the next prospective clinical trial for DNMB. The significant molecular heterogeneity noted in MB is currently under further investigation. A recent publication has described homogeneity at the transcriptome level when multiple biopsies were performed in each MB, which is at odds with the significant differences noted in somatic mutations at the genetic level for the same set of tumors. There are multiple reports of subtypes within the four transcriptional subgroups of MB. Some groups have described transcriptional and genetic differences within the SHH subgroup. In a meta-analysis of 550 MB cases, Kool et al reported a significant difference between the molecular subgroups and their occurrence within each histological variant. In infants with DNMB, 39 out of 44 (89%) were classified as SHH subgroup, which means that around 10% of infants with DNMB might fall into group 3 or 4. We also understand that some SHH tumors do exhibit gain of 3q, loss of 10q and 17p aberrations; all were associated with worse outcomes in infants less than 4 years of age, and therefore may require more intensive therapy. While it is rare to have TP53 mutated tumors in this age group, those that do are predicted to have a poor prognosis. Michael Taylor’s group has integrated DNA methylation profiling with gene expression analysis and identified four distinct SHH subgroups. Infant SHH tumors were mainly distributed across SHH β and SHH γ. SHH β tumors were metastatic, with multiple focal amplifications, and had a worse overall survival compared with SHH γ tumors, which were not associated with any recurrent amplifications and had better outcomes. Desmoplastic histology was
spread over the four subgroups, while SHH γ was the only group with MBEN⁴⁸. Moreover, further
delineation of the genetic landscape of infant SHH MB may help identify specific subgroups that do not respond to chemotherapy-only strategies. Accordingly, it is imperative to include these molecular markers and possible SHH subgroups in the design of future prospective clinical trials for DNMB.

The current available therapy options for DNMB are still limited to high dose chemotherapy with AuHCR or intraventricular methotrexate. The optimal treatment for patients with R0M0 DNMB is still under investigation as we await the long-term toxicity of intrathecal MTX administration, as well as the tumor location, metastasis or patterns of recurrence for those patients who recurred on ACNS1221 and SJYC07. Future trials may also include: (a) dose intensification with tandem consolidation transplants, (b) incorporation of intraventricular/intrathecal chemotherapy along with oral metronomic therapies, (c) introduction of different maintenance regimes, e.g. temozolomide/topotecan/bevacizumab, and (d) ultimate identification and incorporation of molecularly targeted therapies.

Conclusions:

The initial reports of excellent outcomes in DNMB have encouraged multiple co-operative groups to try and reduce the dose or completely eliminate RT from their treatment regimens. However, the increased incidence of tumor recurrences on the chemotherapy-only COG protocol ACNS1221 raised multiple questions on whether DNMB patients can do well with these RT-sparing strategies. Prospective clinical trials specifically designed to include DNMB patients are warranted, and therapy may need to be intensified according to the presence of residual or metastatic disease as well as TP53 mutations and specific chromosomal aberrations. Nonetheless, high dose chemotherapy with AuHCR and chemotherapy regimens incorporating intraventricular MTX are still the main therapy options for patients with DNMB.
Compliance with Ethical Standards:

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Disclosure of potential conflicts of interest:

All the authors declare no conflicts of interest

Research involving human participants and/or animals:

This article does not contain any studies with human participants or animals performed by any of the authors

References:


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<tr>
<th>Clinical Trial</th>
<th># DNMB</th>
<th># MBEN</th>
<th>Radiation</th>
<th>Chemotherapy</th>
<th>IV MTX</th>
<th>AuHCR IO MTX</th>
<th>OS (%) ± SD</th>
<th>EFS/PFS (%) ± SD</th>
<th>References</th>
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<tbody>
<tr>
<td>HIT-SKK’87</td>
<td>4</td>
<td>5</td>
<td>CSI at 3 yrs (35.2 Gy) or tumor progression (24 Gy)</td>
<td>PCB, IFO, VP-16, CDDP, VCR, Ara-C &amp; HD MTX</td>
<td>Yes</td>
<td>No</td>
<td>88.9 ± 10.5 (10 yr)</td>
<td>88.9 ± 10.5 (10 yr)</td>
<td>[17,18]</td>
</tr>
<tr>
<td>HIT-SKK’92</td>
<td>13</td>
<td>7</td>
<td>RT if &lt; a CR at 18 months of age</td>
<td>CPM, MTX, VCR, Carbo &amp; VP-16</td>
<td>Yes</td>
<td>Yes</td>
<td>95 ± 5 (8 yr)</td>
<td>85 ± 8 (8 yr)</td>
<td>[17,18]</td>
</tr>
<tr>
<td>HIT-SKK’2000</td>
<td>13</td>
<td>6</td>
<td>If &lt; CR &amp; ≥18 months; CSI (24 Gy &amp; 54.6 Gy posterior fossa boost); Consolidation: CDDP, CCNU &amp; VCR</td>
<td>CPM, VCR, MTX, Carbo, VP-16 &amp; IO MTX. Once in CR; CPM, VCR, Carbo &amp; VP-16</td>
<td>Yes</td>
<td>Yes</td>
<td>100 (5 yr)</td>
<td>90 ± 7 (5 yr)</td>
<td>[19]</td>
</tr>
<tr>
<td>Head Start I &amp; II</td>
<td>3</td>
<td>0</td>
<td>CSI (23.4 Gy) &amp; tumor boost if &gt; 6 years or with evidence of residual disease</td>
<td>Induction: CPM, VP-16, CDDP &amp; VCR. Consolidation: thiopeta, VP-16 &amp; Carbo</td>
<td>No</td>
<td>Yes</td>
<td>78 ± 14 (5 yr)</td>
<td>67 ± 16 (5 yr)</td>
<td>[16]</td>
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<td>Head Start III</td>
<td>27</td>
<td>0</td>
<td>CSI (23.4 Gy) &amp; tumor boost if &gt; 6 years or with evidence of residual disease at the end of induction</td>
<td>Induction: VCR, CDDP, CPM, VP-16 &amp; HD MTX alternating with VCR, CPM, VP-16 &amp; TMZ. Consolidation: thiopeta, Carbo &amp; VP-16</td>
<td>Yes</td>
<td>Yes</td>
<td>89 ± 6 (5 yr)</td>
<td>89 ± 6 (5 yr)</td>
<td>[21,31]</td>
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<tr>
<td>CCG-99703</td>
<td>14</td>
<td>0</td>
<td>No RT if CR</td>
<td>Induction: CPM, VCR, VP-16 &amp; CDDP. Consolidation: Carbo &amp; thiopeta</td>
<td>No</td>
<td>Yes</td>
<td>85.7 ± 9.4 (5 yr)</td>
<td>78.6 ± 11 (5 yr)</td>
<td>[27]</td>
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<td>CCG-9921</td>
<td>22</td>
<td>0</td>
<td>36 Gy CSI &amp; 54 Gy tumor boost if &gt; 3 yrs, 23.4 Gy CSI &amp; 45 Gy tumor boost if 1.5 to 2.9 years - only for metastatic or residual tumor</td>
<td>Regimen A: VCR during RT then VCR, CCNU &amp; Pred. Regimen B: 8-in-1 (VCR, Methylprednisone, CCNU, HU, PCB, CDDP, CPM &amp; Ara-C)</td>
<td>No</td>
<td>No</td>
<td>85 ± 8 (5 yr)</td>
<td>77 ± 9 (5 yr)</td>
<td>[26]</td>
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<tr>
<td>CNS 9204</td>
<td>10</td>
<td>7</td>
<td>No RT except at progression</td>
<td>Carbo, VCR, MTX, CPM &amp; CDDP</td>
<td>Yes</td>
<td>No</td>
<td>52.9 (5 yr)</td>
<td>35.3 (5 yr)</td>
<td>[22]</td>
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<tr>
<td>P9934</td>
<td>39</td>
<td>0</td>
<td>Conformal RT (18 or 23.4 Gy) to the posterior fossa</td>
<td>Induction: CPM, VCR, CDDP &amp; VP-16. Maintenance: CPM, VCR &amp; VP-16</td>
<td>No</td>
<td>No</td>
<td>79 ± 7 (4 yr)</td>
<td>58 ± 8 (4 yr)</td>
<td>[26]</td>
</tr>
<tr>
<td>POG 9233/34</td>
<td>20</td>
<td>0</td>
<td>CSI (27-38.5 Gy) for metastatic disease or &lt; CR at end of chemotherapy</td>
<td>Randomized* Baby POG-1** vs an intensified regimen (doubling CPM dose &amp; increasing CDDP &amp; VP-16 frequency)</td>
<td>No</td>
<td>No</td>
<td>Not provided</td>
<td>34 ± 11 (4 yr)</td>
<td>[24,25]</td>
</tr>
<tr>
<td>SJYC07</td>
<td>23</td>
<td>0</td>
<td>None</td>
<td>Induction: MTX, VCR, CDDP &amp; CPM. Consolidation: Carbo &amp; VP-16. Oral maintenance: CPM, Topo &amp; erlotinib</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>87% (5 yr)</td>
<td>60% (5 yr)</td>
</tr>
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</table>

DNMB, Desmoplastic nodular medulloblastoma; MBEN, Medulloblastoma with extensive nodularity; CSI, Craniospinal irradiation; AuHC, Autologous hematopoietic stem cell rescue; IO, Intraomma; MTX, Methotrexate; OS, Overall survival; SD, Standard deviation; EFS, Event-free survival; PFS, Progression-free survival; PCB, Procarbazine, IFO, Ifosfamide; VP-16, Etoposide; CDDP, Cisplatin; VCR, Vincristine; Ara-C, Cytarabine; HD-MTX, High-dose methotrexate; RT, Radiation therapy; CR, Complete remission; CPM, Cyclophosphamide; Carbo, Carboplatin; CCNU, Lomustine; HU, Hydroxyurea; Topo, Topotecan

* Baby POG 1: VCR and CPM (A), CDDP and VP-16 (B) in an AABAAB sequence