



High-dose chemotherapy and craniospinal irradiation-sparing approach for WNT medulloblastoma of early childhood

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Abstract

Background Adjuvant chemotherapy and craniospinal irradiation led to excellent survival in older children (≥ 3 years) with WNT medulloblastoma, allowing for ongoing careful treatment de-escalation. However, treatment with standard dose chemotherapy alone or in combination with involved field radiotherapy to the tumor bed only had high rates of distant treatment failure. In younger children, WNT medulloblastomas are extremely rare and the survival following high-dose chemotherapy (HDC) and radiation-sparing strategies has not been reported.

Patients and methods Through international collaboration, we assembled a cohort of young children with WNT medulloblastoma treated with HDC and craniospinal irradiation avoidance to describe their survival and neurocognitive and ototoxicity profile.

Results Five patients, diagnosed at median age of 7.0 years (range 2.7–7.5) underwent HDC and autologous stem cell transplantation. None of them received adjuvant radiotherapy. All patients were alive beyond four years from diagnosis. Evaluated patients had neurocognitive abilities reported within low average to average range.

Conclusion In this cohort, the survival of young children with WNT MB treated with HDC alone was excellent. The rare possibility of a molecular diagnosis of WNT MB in early childhood should not be viewed as an exclusion criterion to enroll on infant brain tumor strategies relying on HDC consolidation.

Clinical trial number Not applicable.

Keywords WNT medulloblastomas · High-dose chemotherapy · CSI avoidance

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Table 1 Patients characteristics

N	Sex/Age (yrs)	Meta-static status	Extend of resection primary site	Histology	Molecular characterization	HD MTX during induction	HDC regimen	Status at end of therapy	Status at last FU (yrs)
1	F/7.0	M0	GTR	Classic NOS	WNT (Nano string, gene confidence=1)	No	3 x CB THIO	CCR	ANED/7.4
2	F/4.8	M0	GTR	Classic NOS	WNT (Nano string, gene confidence=1)	Yes	1 x TEC	CCR	ANED/4.7
3	M/2.7	M0	GTR	Classic NOS	WNT CTNNB1mut	No	3 x CB THIO	CCR	ANED/8.6
4	M/7.3	M2	STR	Classic NOS	WNT CTNNB1mut	Yes	1 x TEC	CR	ANED/4.3
5	F/7.5	M3	STR	Classic NOS	WNT CTNNB1 mut	No	3xCB THIO	CR	ANED/7.1

ANED: alive with no evidence of disease; CB: Carboplatin; CR: complete remission; CCR: continuous complete remission; F: Female; FU: follow-up; GTR: gross total resection; HD MTX: high-dose methotrexate; HDC: high-dose chemotherapy; M: male; M0: non metastatic; M2: Brain metastasis; M3: spinal metastasis; THIO: thiotepa; TEC: thiotepa, etoposide, carboplatin; STR: subtotal resection

Background

Among the four molecular subgroups described in medulloblastoma (MB), WNT subgroup is mainly seen in older children (median age of 9 years) [1]. While the WNT subtype is reported in 15% of adult MB [2], it is extremely rare in early childhood. Occasional WNT MB have been identified retrospectively through molecular characterization of medulloblastoma cohorts in young children [3, 4] but very little is known about their management at this young age, where treatment strategies aim at minimizing the deleterious neurocognitive effect associated with craniospinal irradiation (CSI).

Patients and methods

We retrospectively assembled a cohort of young children, aged 7 years or younger, diagnosed between 2001 and 2023 with WNT medulloblastoma and treated with myeloablative high-dose chemotherapy (HDC) and a CSI-sparing approach to describe their outcome. Patients treated with adjuvant involved-field radiotherapy (IFRT) were eligible to study. Following institutional review board approval at each participating center, patient's demographic, institutional pathology and molecular report, initial treatment and management at relapse and outcome data were collected.

Descriptive statistics were performed using median and range for continuous variable and counts and percentages for categorical variable analysis.

Results

Through international collaboration reaching out to 29 centers using HDC for young children with medulloblastoma, we identified five patients (two males, three females) diagnosed with a WNT MB and treated with a high-dose chemotherapy strategy. The median age at diagnosis was 7.0 years (range 2.7–7.5) with two of them under the age of 5 years at diagnosis. Two patients had metastatic disease at diagnosis and did not achieve an initial complete resection of their primary tumor. The WNT subgrouping was obtained from the institutional report. Details on the method of molecular characterization were available for all patients. CTNNB1 somatic mutation was detected in three samples by Sanger sequencing or methylation array and the two remaining ones were identified through nanostring gene expression analysis. All patients were treated using North American infant protocols with HDC regimens (as per ACNS0334 or CCG99703 or Head Start protocols) [5–7]. The reasons to proceed with infant strategy for the three children older than 5 years old at diagnosis were parental refusal of adjuvant CSI in two and institutional preference for the latest one. High-dose methotrexate (HD MTX) was used during induction in two patients treated on Head Start protocols. Three patients underwent consolidation with three sequential cycles of high-dose carboplatin and thiotepa and two received only one cycle of consolidation with high-dose thiotepa, carboplatin and etoposide (TEC). While the use of focal RT was allowed as part of the eligibility criteria, none of the patients identified had undergone adjuvant IFRT. None of the patients underwent intrathecal chemotherapy or maintenance therapy following consolidation.

At completion of initial therapy, all patients were in complete or continuous complete remission. (Table 1)

All five patients remained alive without evidence of disease at a median follow-up time of 7.2 years (range 4.3–8.6) from diagnosis.

Audiologic evaluations were available for three patients, indicating post treatment, two grade 0 and one grade 1 ototoxicity according to the SIOP Boston grading system. Neurocognitive evaluations were available for three patients. One patient assessed at 14 years of age (seven years from initial diagnosis) displayed broadly low-average intellectual ability with exceptionally low working memory, low average processing speed and struggled with reading, writing and math. The second patient assessed at 9 years of age (two years from initial diagnosis) had intellectual functions within average for age but displayed low average scores for verbal comprehension, working memory and processing speed along with hyperactivity. The third patient evaluated at 7 years of age (four years from initial diagnosis) displayed average intellectual, verbal/language and visual-spatial abilities with a reported full-scale IQ at the 63rd percentile.

Discussion

WNT MB accounts for approximately 15% of all newly diagnosed medulloblastoma patients. However, this molecular subtype is extremely rare in young children [8, 9]. In a cohort of 93 patients with WNT MB, the median age at diagnosis was 10 years (range 2–56.3), and among them only four (5.3%) were 5 years of age or younger at initial diagnosis [3]. The recent molecularly informed North American clinical trials for infants under the age of 3 years, namely the ACNS 0334 and the SJYC07, did not identify any WNT MB patient in either of their cohorts [5, 10].

WNT MB are highly curable when treated with CSI followed by adjuvant chemotherapy. The most recent prospective trials in older children have reported excellent progression free survival (PFS) and overall survival (OS) for non-metastatic WNT MB. In the ACNS0331 trial for average-risk MB, the 5 years event free survival (EFS) for the 64 patients with WNT MB was 93.3% (95% CI, 86.8 to 99.8). In the subgroup of 19 children less than 8 years old at diagnosis, no significant difference in EFS was observed according to the dose of CSI administered (low dose of CSI of 18 Gy versus standard dose of CSI of 23.4 Gy) [11]. Even for the 14 patients with high-risk WNT MB treated with 36 Gy CSI followed by adjuvant chemotherapy on the ACNS 0332 trial, the 5y EFS was 92.9% (95% CI, 75.7%–100%) [12].

Considering the excellent outcome for this subgroup of MB, careful de-escalation of the CSI dose has been tested in three recent prospective trials. From the preliminary report of the SJMB 12 trial, the 74 patients treated on the stratum W1 (WNT, M0, R0, classic histology and chromosome 6

monosomy) with a CSI dose of 15 Gy followed by 4 courses of adjuvant chemotherapy, achieved a 5-year PFS and OS 90.4% (\pm 5.1%) and 98.6% (\pm 2.1), respectively. The pattern of relapse included two locals, one disseminated and one combined relapse [13]. Similarly, the initial results of treatment de-intensification on the SIOP PNET MB 5 trial for 82 low-risk WNT patients, treated with 18 Gy CSI and six cycles of chemotherapy, indicated a 3-year event free survival of 88.7% (\pm 6.9) for the intent to treat cohort [14] [NCI02066220]. The recently closed COG ACNS1422 [NCI02724579] and the ongoing prospective trial, FOR-WNT 2 [NCT04474964], are also evaluating decreasing the dose of CSI to 18 Gy for low-risk group of WNT. Concomitant decrease in the cumulative dose of chemotherapy during radiotherapy and during maintenance phase was also part of the de-escalation strategy on the ACNS1422 trial.

However, the attempt to fully eliminate CSI in older children with WNT MB has not been successful. Cohen et al. reported their experience of completely omitting RT for patients with low-risk WNT MB (non-anaplastic, non-metastatic, with GTR or NTR) by treating them with conventional chemotherapy only, according to the ACNS 0331 regimen [15]. Six patients were enrolled and five of them completed therapy. The study closed prematurely as the first two patients relapsed shortly after completion of chemotherapy with local and disseminated recurrence. Overall, three of the six patients relapsed and underwent salvage therapy with CSI and chemotherapy. Out of the three patients who did not relapse, two underwent adjuvant CSI at the dose of 23.4 Gy post chemotherapy and one proceeded to consolidation with HDC and autologous stem cell transplantation. This latter patient subsequently developed myelodysplastic syndrome requiring allogeneic bone marrow transplantation and remained in continuous complete remission at 5 years from original WNT MB diagnosis. Overall, four patients were alive with no evidence of disease at more than 3 years from diagnosis, and one patient died of progressive disease. Gupta et al. from the Tata Memorial Centre described seven patients with low-risk WNT MB treated with post operative IFRT (54 Gy) followed by six cycles of adjuvant conventional chemotherapy. This study also closed early as three patients presented with disseminated relapses at respectively 15-, 21-, and 23-months post diagnosis. All three were successfully salvaged with chemotherapy and CSI delivered at doses ranging from 35 to 40 Gy. While the number of treatment failures was considered unacceptable for this subgroup of favorable MB, the study nevertheless described three patients (42%) who did not relapse despite the omission of CSI, who were alive at 42-, 35- and 35-months post diagnosis, a timeline away from the reported median time to relapse of 18 months for WNT

MB [16, 17]. To further support the importance of early adjuvant CSI, the authors quoted the analysis from the National Cancer Database by Kann et al. to highlight the fact that younger children (3 to 8 years) diagnosed with medulloblastoma and treated with deferred radiotherapy had worse survival compared to those who received radiotherapy upfront [18]. However, molecular subtypes and the details of the modalities of chemotherapy administered (conventional or high-dose chemotherapy) in this cohort of younger patients were not described.

To our knowledge, upfront treatment with HDC consolidation in the younger group of patients with WNT MB has not been reported previously, as children with WNT MB are generally older at diagnosis and therefore very unlikely to be exposed to radiation-sparing strategies. Consolidation with HDC is part of the infant brain tumor strategies to avoid or delay the use of cranial radiation in this more vulnerable population in terms of neurocognitive impairment. In older patients, adjuvant CSI is considered standard of care for MB and report on HDC in this older group remains confidential. The Head Start 4 is the only clinical trial in the molecular era, using HDC consolidation for patients aged up to 10 years. In the low-risk arm of this trial, for the SHH and WNT MB, adjuvant radiotherapy was not part of the treatment. Waiting for data maturation, this trial may provide additional descriptive data for the 3 to 10 years old patients with WNT MB [NCT02875314]. There is currently no comparison of older children's strategies with HDC approaches that can be made. Our series was assembled from a cohort of young children treated with HDC-based infant strategies, who were identified on a post hoc molecular evaluation to have WNT MB. Hence, the indication of consolidation with HDC was not driven by their underlying WNT subgroup. Although our case series is limited to five patients, all of them were long-term survivors, free of relapse with a median follow-up time of 7.2 years (range 4.3–8.6) from diagnosis.

Our series, along with the patient described by Cohen et al., who after conventional chemotherapy, underwent consolidation with HDC instead of CSI, suggests that some patients with WNT MB are amenable to cure without adjuvant CSI, provided they undergo consolidation with HDC [15]. It is interesting to note that two of our patients with metastatic disease and subtotal resection of their tumor achieved a complete response at the end of consolidation with HDC. Preclinical studies have previously indicated WNT MB, unlike other molecular subtypes, lacks blood brain barriers, conferring exquisite sensitivity to chemotherapy [19]. Furthermore, chemotherapy regimens including cumulative dose of cyclophosphamide greater or equal to 12 g/m² have been

associated with a significantly lower risk of relapse [3]. The absence of blood barrier combined to a cyclophosphamide equivalent dose (CED) of 50 for thiopeta used in the conditioning regimen of North American HDC strategies likely contribute to the excellent response and survival we observed in our cohort [20]. We did not collect for our patients, information on potential additional molecular alterations within the WNT subgroup such as the presence of monosomy 6, the MYC/MYC_N status or the more recently described negative impact of TP53 and OTX2 alterations [21]. This constitutes a limitation to evaluate the interplay between treatment intensity and molecular risk factors. It is very unlikely that future prospective clinical trials for infant MB will enroll enough children with WNT to decipher the role of these alterations in the context of HDC.

While the intent of this report is not to dismiss the major contribution of CSI to the excellent outcome of WNT MB in older children [22], it raises the question of HDC as an alternative to CSI for the rare young patients, for whom CSI, even at reduced dose, may have a significant impact on their neurocognitive outcome. Limited studies have documented the neurocognitive outcome of young children treated with a lower dose of CSI (≤ 18 Gy CSI) [23]. From the ACNS 0331 clinical trial, Michalski et al., described a continuous neurocognitive decline in younger patients aged 3 to 7 years treated with both low dose and standard dose of CSI (18 and 23.4 Gy respectively). Patients treated with standard-dose CSI had, however, a steeper decline in neurocognitive ability than those treated with low-dose CSI, when comparing time point assessments at 9 months and 30 months post diagnosis [11]. In our limited series, the three patients tested had intellectual abilities within normal range. If patient's number permits, specific report of the neurocognitive outcome of the younger children with WNT MB treated on the SJMB12 trial with 15 Gy CSI will add valuable information to the attempt to compare these different strategies within the young age group.

The age cut-off for the definition of infants has been raised from 3 years to 4 years for the SHH iMB in several prospective trials without jeopardizing the excellent survival when treatment regimens rely on either HDC or conventional chemotherapy and serial injection of intraventricular chemotherapy [7, 24]. The acceptable upper age limit for HDC as an alternative to CSI for WNT MB remains unclear, given the expected excellent outcome in low-risk patients treated with lower dose of CSI. As upfront molecular characterization is becoming more routine for MB, we anticipate more WNT MB will be identified in early childhood and may raise discussion about acceptable therapeutic approaches for this age

group. Our limited experience may support the consideration for HDC strategies in patients under the age of 4 or 5 years. The toxicity profile of HDC regimens also needs to be taken into consideration, notably the risk of infertility and ototoxicity. The North American conditioning regimens using high-dose of thiotepa bring the cumulative cyclophosphamide equivalent dose (CED) significantly above the accepted 7.5 g/m² (45 to 90 g/m²) for developing fertility impairment and infertility. Similarly, previous report on ototoxicity profile associated with high-dose carboplatin-based consolidation following heavy cisplatin-based induction in young children indicated clinically significant hearing impairment in 45% of the patients and 39% of them requiring hearing support [25]. While no specific report has focused to date on the risk of second malignancies associated with these HDC regimens, their high CED may also increase the risk of second neoplasms. Those risks therefore need to be carefully weighed against the risks of neurocognitive impairment from CSI when guiding treatment recommendations.

Conclusion

In this limited case series of young children with WNT MB, the survival following HDC alone without adjuvant RT was excellent. The rare possibility of a molecular diagnosis of WNT MB in young children should not be viewed as an exclusion criterion to enroll on infant brain tumor strategies relying on HDC consolidation.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval The study was approved by the Health Research Ethics Board of Alberta Cancer Committee (HREBA.CC-23-0060).

Human ethics and consent to participate Not applicable.

Competing interests The authors declare no competing interests.

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