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Cumulative dose of chemotherapy and survival outcomes in children with average-risk medulloblastoma treated on Children's Oncology Group study ACNS0331

Erin Wright, Catherine Billups, Sarah Rush, Yimei Li, Anna Janns, Jeff M. Michalski, Ralph Salloum, and Peter de Blank

All author affiliations are listed at the end of the article

Corresponding Author: Erin Wright, MD, Department of Hematology and Oncology, Akron Children's Hospital, 1 Perkins Sq., Akron, OH 44308 (ewright@akronchildrens.org).

Abstract

Background. Although survival outcomes for average-risk (AR) medulloblastoma remain excellent, patients experience significant long-term toxicities. To evaluate the effect of therapy dose modifications among children with AR medulloblastoma, we examined the association of cumulative chemotherapy dose with overall survival (OS) and event-free survival (EFS) for patients treated on Children's Oncology Group (COG) study ACNS0331.

Methods. A cohort of children enrolled on ACNS0331 (medulloblastoma confirmed by methylation, received standard dose craniospinal radiation, and completed all cycles of chemotherapy) were evaluated for cumulative chemotherapy dose intensity continuously and categorically (≥75% or <75% of planned dose). Cox proportional hazards regression models were used to examine associations of proportion of planned chemotherapy received with outcome. A secondary analysis separately evaluated each of the 4 molecular subgroups: Wnt-activated (WNT), Sonic Hedgehog Activated (SHH), group 3 and group 4.

Results. Two hundred thirty-five children were followed for a median of 9.3 years (range, 7.0-10.4). Dose intensities of vincristine (VCR) and cisplatin showed the most variability (17% and 23.8% of patients received <75% of expected dosing, respectively). Molecular subgroup remained a significant predictor of outcome (EFS [P=.012] and OS [P=.008]). Cyclophosphamide and lomustine were not examined due to minimal dose variability. No significant differences in EFS or OS were found related to reduced dose intensity for VCR (P=.49 EFS, P=.52 OS) or cisplatin (P=.36 EFS, P=.35 OS) when analyzed independently. There was no difference in the effect of dose reductions by molecular subgroup.

Conclusions. Moderate dose reductions of at least 25% in VCR and cisplatin do not significantly affect survival in AR medulloblastoma. Effects of larger dose reductions (>50%) or dose reductions in high-risk disease were not studied.

Key Points

- Reduced dose intensity (<75% planned dose) cisplatin or vincristine resulted in similar survival compared to planned dose (>75%) intensity.
- Within appropriate patient populations, careful dose adjustments of chemotherapy may be considered.

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Importance of the Study

Children with average-risk medulloblastoma have excellent long-term survival, yet many experience debilitating chemotherapy-related toxicities such as neuropathy and hearing loss. Reducing exposure to agents like vincristine (VCR) and cisplatin may help mitigate these effects, but the impact of dose reductions on survival has remained unclear in contemporary treatment protocols. Using data from the Children's Oncology Group study ACNS0331, this study evaluates the relationship between cumulative chemotherapy dose and survival outcomes in a well-characterized cohort. We found that moderate reductions in VCR and cisplatin dose intensity did not significantly affect event-free or overall survival in the overall cohort or within molecular subgroups. These findings may be reassuring to physicians and patients that appropriate dose reductions rarely reduce therapeutic efficacy. Our results can help inform future clinical trial designs that aim to maintain survival outcomes while minimizing treatment burden and improving quality of life for survivors of pediatric medulloblastoma.

Medulloblastoma is the most common malignant pediatric brain tumor, occurring in approximately 1:100 000 pediatric patients.[1] Treatment relies on maximal safe surgical resection, craniospinal radiation, and systemic chemotherapy, but often comes with long-term side effects and chronic health conditions. Craniospinal radiation is particularly associated with cognitive deficits that limit its use in developing children less than 3 years of age.[2–5] Chemotherapy following craniospinal radiation for average-risk (AR) medulloblastoma consists of a combination of platinum-based agents in conjunction with vincristine (VCR), lomustine (CCNU), and cyclophosphamide (CPM) that can also cause chronic adverse events. While 5-year overall survival (OS) among children with AR medulloblastoma nears 85%, survivors are frequently left with significant morbidities from therapy, including learning difficulties, endocrine abnormalities, growth issues, and hearing loss.[6–9]

Current therapeutic trials aim to maximize treatment efficacy for high-risk groups while minimizing treatment-related side effects in lower risk groups. Vincristine and cisplatin are frequently used agents in the treatment of medulloblastoma. Vincristine, an inhibitor of microtubule polymerization, may cause significant neurotoxicity, leading to neuropathic pain, peripheral muscle weakness, seizures, cranial neuropathies, motor weakness, and constipation from autonomic neuropathy.[10–13] Cisplatin, which interrupts DNA repair, also has negative systemic effects and neurotoxicity, the most prominent being its impact on hearing.[14] These side effects can persist long after patients complete therapy and affected nerves may continue to show electrophysiologic dysfunction even after recovery.[15,16]

Efforts have been made over the years to reduce the total dose of these agents to mitigate therapeutic side effects with mixed results. For example, reports have shown that patients with Charcot-Marie-Tooth disease, who have severe peripheral neurotoxicity associated with VCR, have been cured of medulloblastoma using regimens that omit this drug entirely.[17–19] The limited CSF penetration of VCR have lead to questions regarding its importance in medulloblastoma therapy[20,21]; however, VCR remains a standard agent in conventional medulloblastoma treatment. Previous reports have shown that modest dose reductions in cisplatin do not affect OS, but these studies used different regimens than the current standard risk protocols.[9] However, while dose modifications may help decrease side effects, they can also negatively impact OS.[22,23]

Understanding the effect of cumulative chemotherapy dose on survival in children with medulloblastoma would help guide future clinical trial development to maximize survival and minimize long-term effects of therapy. To evaluate the effect of dose modifications among children with standard-risk medulloblastoma, we examined the effect of cumulative chemotherapy dose on OS and event-free survival (EFS) retrospectively using previously published data from children enrolled in the Children's Oncology Group (COG) study ACNS0331.[24] Following the opening of ACNS0331, medulloblastoma has additionally been defined by 4 diagnostic groups by methylation profiling (WNT-activated (WNT), Sonic Hedgehog Activated (SHH), group 3, group 4) with varied prognosis and potentially divergent therapies.[25] We therefore also examined the association between cumulative chemotherapy dose and EFS/OS by medulloblastoma group (WNT, SHH, group 3, group 4) in the same patient cohort.

Methods

Patients and Eligibility

We evaluated the cumulative doses of chemotherapy and survival outcomes (OS and EFS) for patients enrolled in the most recent COG study for AR medulloblastoma (ACNS0331). Similar to the eligibility criteria outlined in ACNS0331, patients were eligible for review if they were between the ages of 3 and <22 years at the time of diagnosis, had histologically confirmed newly diagnosed medulloblastoma, appropriate baseline organ and physical function, and, in accordance with AR criteria, had residual tumors <1.5 cm^2 on MRI with no evidence of metastatic disease or diffuse anaplasia.[21] Patients were not eligible if they had previously received antineoplastic therapy.

Among all subjects on ACNS0331, certain participants were excluded from analysis (Figure 1). Individuals randomized to low-dose craniospinal radiation (of 18 Gy) were excluded due to known inferior outcomes. Patients were included only if medulloblastoma was confirmed by methylation profiling. Eighteen patients were excluded due to nonmedulloblastoma or inconclusive methylation results, and 84 were excluded due to insufficient tissue for methylation analysis. Without confirmed diagnosis, these cases

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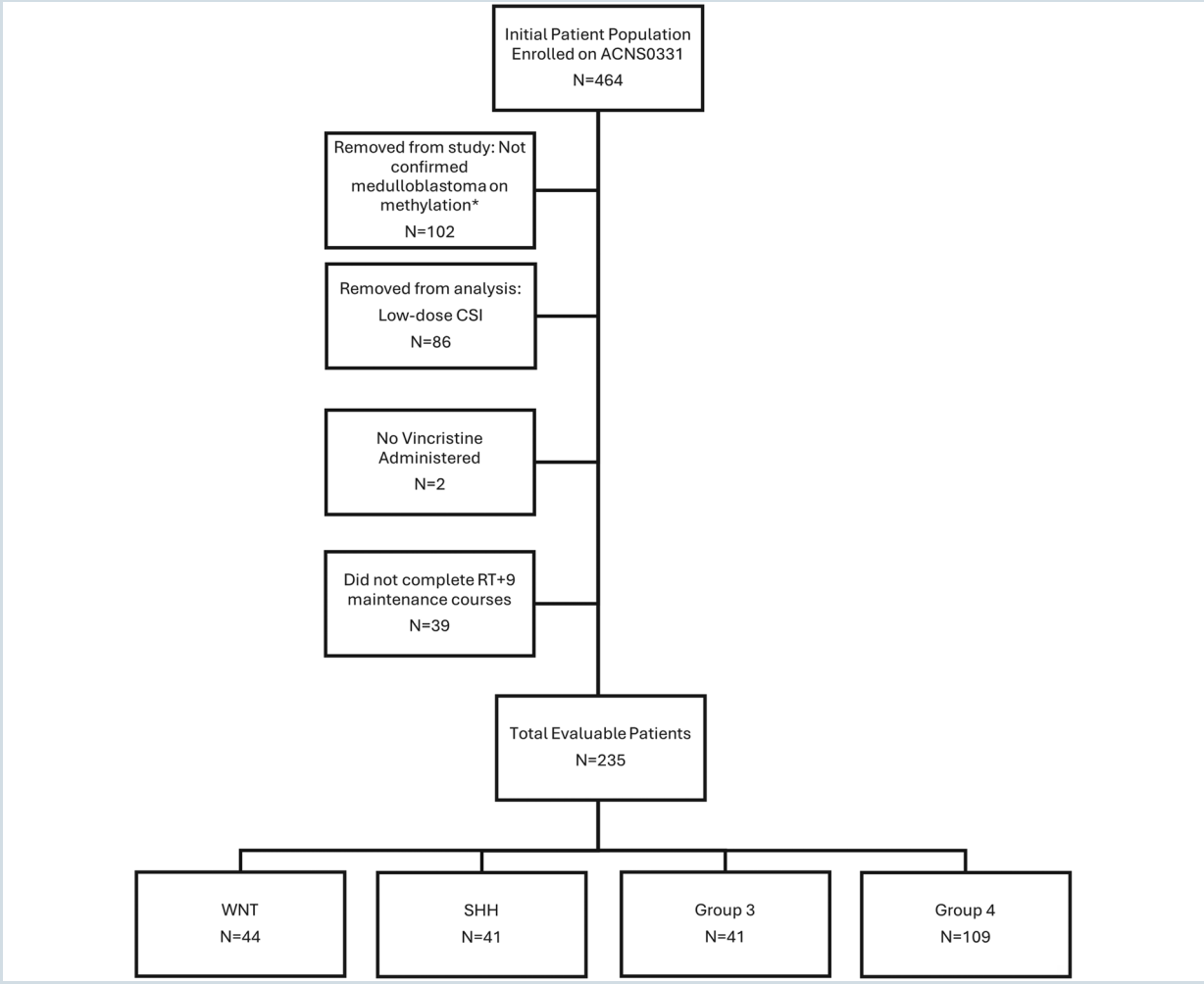

Figure 1. Patient inclusion criteria. Due to the known differences in outcome between medulloblastoma and other embryonal tumors, only patients with confirmed medulloblastoma on methylation were included in our analysis.[26] *This included patients with inconclusive or nonmedulloblastoma methylation results ($N=18$) as well as those without enough tissue to perform methylation ($N=84$).

could not be reliably evaluated and were excluded to maintain cohort integrity. Finally, this analysis was limited to patients who completed all courses of radiation and chemotherapy. The cohort was restricted to patients that completed therapy to ensure patients that stopped therapy early due to progressive disease, started a new therapy not captured in the ACNS0331 dataset, or were lost to follow-up did not influence the analysis. A secondary analysis included the cohort that did not complete all courses of chemotherapy.

Medulloblastoma methylation group (WNT, SHH, group 3, group 4) was determined from fresh-frozen or formalin-fixed paraffin-embedded tissue samples using Illumina Infinium Methylation EPIC BeadChip arrays as previously described.[24] Chemotherapy dose intensity was analyzed continuously and categorically (≥75% or <75% of the planned dose) for each agent. The percent of the planned dose for each patient was calculated as cumulative dose received (for each drug in mg/m^2) divided by the total planned dose, multiplied by 100%. Total planned doses were determined based on the protocol: VCR 45 mg/m^2 (maximum 2 mg per dose or 48 mg total), cisplatin 450 mg/m^2, CPM 6000 mg/m^2, and CCNU 450 mg/m^2.

Statistical Analysis/Analysis Plan

Fisher's exact and chi square tests were used to compare categorical variables among patient groups. The Wilcoxon-Mann-Whitney test was used to compare continuous variables (eg, age) among patient groups. Event-free survival was defined as the time interval from date of study entry to date of disease progression, disease recurrence, second malignant neoplasm or death from any cause, whichever occurred first, or to the date of last follow-up for patients without events. Overall survival was defined as the time interval from date of study entry to date of death from any cause or to the date of last follow-up for survivors. Patients were categorized into 2 cumulative dose groups based on the percentage of planned dose received (≥75% vs <75%). event-free survival and OS were estimated using the method of Kaplan and Meier, and log rank tests were used to compare outcome distributions by groups. Cox proportional hazards regression models were used to examine associations of percentages of planned drugs received with outcome. Analyses were restricted to eligible, evaluable

patients who received chemoradiation and all 9 maintenance cycles. In secondary analyses, eligible and evaluable patients who started VCR but did not receive all 9 courses of chemotherapy were included, and Cox regression models were used to examine the association between accumulating VCR and cisplatin doses and outcome; dose was a time-dependent covariate in these models. No power or sample size calculations were done as this was an exploratory analysis of a completed study.

Results

Two hundred thirty-five patients completed all planned chemotherapy and were included in analyses (Table 1). The median follow-up was 9.3 years (Interquartile Range (IQR), 7.2-10.4 years). Vincristine and cisplatin showed the most variable dose intensity of the chemotherapy agents. Almost a quarter of patients (23.8%) received less than 75% of the expected cisplatin dosing based on protocol, and 17% of patients received less than 75% of VCR dosing (see Supplementary Table S1). Of note only one patient received less than 50% of the recommended cisplatin dose and only 9 patients received less than 50% of the recommended VCR dose. Cyclophosphamide and CCNU were excluded from analysis because dose variability was considerably lower: only 8 patients (3.4%) and 2 patients (0.9%) received <75% of the planned cumulative dose of CPM and CCNU, respectively.

To investigate differences between patients who received more or less than 75% of the planned dose of VCR and cisplatin, we compared demographic and treatment characteristics (Table 2). No differences were found between cumulative dose groups in terms of sex, race, ethnicity, or radiation volume (involved field vs posterior fossa radiation therapy). There was evidence of a difference in the distribution of molecular subgroup among patients who received <75% vs ≥75% of the planned cisplatin dose (P=.016). Median age at diagnosis was older among patients who received <75% of the planned VCR dose compared to ≥75% planned dose (11.9 vs 9.2 years, P<.001). No difference in age was found between those that received standard vs reduced cisplatin dosing (P=.34).

No significant difference in EFS or OS was found due to reduced dose intensity for VCR (EFS P=.36, OS P=.35) or cisplatin (EFS P=.49, OS P=.52) (Figure 2). As expected, molecular subgroup was a significant predictor of outcome (EFS P=.012, OS P=.008) in the overall cohort (Figure 3). In all 4 molecular subgroups, there was no evidence of a significant difference in outcome by dose reduction group (<75% vs ≥75%) for either VCR or cisplatin (Table 3). While not statistically significant, differences in 5-year EFS were seen among some medulloblastoma groups. The largest nonsignificant differences were observed among SHH patients related to cisplatin dose intensity (EFS of 87.4% vs 64.8%) and group 3 patients related to VCR intensity (EFS of 70.6% vs 50%). When analyzed as continuous variables, there was also no evidence of significant associations between outcome and percentages of VCR and cisplatin received. In additional analyses that included eligible and evaluable medulloblastoma patients who did not receive chemoradiation and all 9 maintenance courses (n=274), there remained no evidence of significant associations between outcome and VCR and cisplatin (see Supplementary Table S2).

Table 1. Patient demographics of individuals who received radiotherapy + 9 courses of chemotherapy (n=235).

Age at diagnosis	
Median	9.8 years
Range	3.2-21.8 years
Sex, N (%)	
Male	148 (63.0)
Female	87 (37.0)
Race, N (%)	
White	197 (83.8)
African American/Black	15 (6.4)
Native Hawaiian or Other	3 (1.3)
Asian	6 (2.6)
American Indian	1 (0.4)
Unknown	13 (5.5)
Ethnicity, N (%)	
Not Hispanic or Latino	182 (77.5)
Hispanic or Latino	44 (18.7)
Unknown	9 (3.8)
Medulloblastoma molecular subgroup, N (%)	
SHH	41 (17.5)
WNT	44 (18.7)
Group 3	41 (17.5)
Group 4	109 (46.3)

Discussion

Overall survival in pediatric medulloblastoma ranges from excellent for low-risk disease to inferior for very high-risk disease.[6,8,9] Understanding the impact of dose intensity can help inform treatment strategies for different risk groups. For lower risk patients, it is crucial to consider reducing chemotherapy doses to minimize short- and long-term late effects.[4,6] Our analysis of children with AR medulloblastoma treated on ACNS0331 shows that significant dose modifications (defined as <75% of the planned dose) of VCR or cisplatin occur in more than a quarter of all patients. Fortunately, EFS and OS were not significantly affected by these dose reductions, suggesting that patients may tolerate a moderate decrease of at least 25% in overall dose intensity of these agents, without sacrificing survival outcomes.

Of note, while reduced chemotherapy was categorized as <75% of the expected dose in this analysis, few patients received less than 50% of the expected dose. While the analysis may support safe dose reduction of VCR and cisplatin of at least 25%, reductions more than 50% were not able to be well investigated. Therefore, this analysis is limited to examining the effect of moderate dose reductions as more severe chemotherapy restrictions may have a different effect.

These finding are consistent with other previous studies. Notably, SJMB03 used significantly lower doses of cisplatin (cumulative dose 300 mg/m^2 vs 450 mg/m^2 in ACNS0331)

Table 2. Patient characteristics by percentage of recommended doses of vincristine and cisplatin received ($n=235$).

	Vincristine cumulative dose			Cisplatin cumulative dose		
	<75% (n=40)	≥75% (n = 195)	P-value	<75% (n=56)	≥75% (n=179)	P-value
Sex, n (%male)	27 (67.5)	121 (62.1)	.59	33 (58.9)	115 (64.3)	.53
Race, n (%)			.48[a]			.63[a]
White	32 (80.0)	165 (84.6)		47 (83.9)	150 (83.8)	
Black	2 (5.0)	13 (6.7)		3 (5.4)	12 (6.7)	
Other	1 (2.5)	9 (4.6)		4 (7.1)	6 (3.4)	
Unknown	5 (12.5)	8 (4.1)		2 (3.6)	11 (6.2)	
Ethnicity, n (%)			.25[b]			.85[b]
Hispanic/Latino	4 (10.0)	40 (20.5)		10 (17.9)	34 (19.0)	
Not Hispanic/Latino	32 (80.0)	150 (76.9)		46 (82.1)	136 (76.0)	
Unknown	4 (10.0)	5 (2.6)		0 (0)	9 (5.0)	
Age at diagnosis (median [range] in years)	11.9 (5.3-21.8)	9.2 (3.2-18.8)	**<.001**	9.5 (3.6-21.8)	10.1 (3.2-18.8)	.34
Radiation type, n (%)			.86			.65
IFRT	18 (45.0)	93 (47.7)		28 (50.0)	83 (46.4)	
PFRT	22 (55.0)	102 (52.3)		28 (50.0)	96 (53.6)	
Medulloblastoma methylation group, n (%)			.39			**.016**
WNT	7 (17.5%)	37 (19.0)		3 (5.4)	41 (22.9)	
SHH	6 (15.0)	35 (18.0)		9 (16.1)	32 (17.9)	
Group 3	4 (10.0)	37 (19.0)		10 (17.9)	31 (17.3)	
Group 4	23 (57.5)	86 (44.1)		34 (60.7)	75 (41.9)	
VCR dose group, n (%)						1
<75% cumulative				9 (16.1)	31 (17.3)	
≥75% cumulative				47 (83.9)	148 (82.7)	
Cisplatin dose group, n (%)			1			
<75% cumulative	9 (22.5)	47 (24.1)				
≥75% cumulative	31 (77.5)	148 (75.9)				

[a]Comparison of White vs Black + Other; unknown category was excluded from this analysis.
[b]Unknown category was excluded from this analysis.

and VCR (cumulative dose 8 mg/m^2 vs 45 mg/m^2 in ACNS0331).[23,24] Despite these lower doses, similar outcomes were observed, although SJMB03 used significantly higher doses of CPM (cumulative dose 16 000 mg/m^2 compared to 6000 mg/m^2 on ACNS0331) and stem cell rescue, making direct comparisons challenging. Similarly, Nageswara Rao et al. reported that cumulative cisplatin dose was not associated with EFS or OS in children with newly diagnosed AR medulloblastoma in a prior AR study (CCG A9961).[9] These results led to a reduction in cumulative cisplatin dose in ACNS0331 (from 600 mg/m^2 in A9961 to 450 mg/m^2 in the ACNS0331). The results of our analysis suggest that cisplatin and VCR may be further reduced in order to reduce late toxicities associated with these chemotherapy agents, such as neurotoxicity and hearing loss. While statistical power is reduced in analyses of individual medulloblastoma methylation groups, no significant differences were found in any molecular subgroup.

Long-term side effects of chemotherapy, particularly ototoxicity and peripheral neuropathy, are significant concerns for medulloblastoma survivors.[27] Ototoxicity can significantly impact the quality of life and studies have shown that higher doses of cisplatin and cochlear irradiation are associated with increased risk of ototoxicity.[27–29] Peripheral neuropathy is another severe long-term side effect secondary to both cisplatin and VCR resulting in neuropathic pain, muscle weakness, and motor dysfunction, which may persist long after therapy completion.[30] These neurotoxic effects can significantly impair the daily functioning and quality of life of survivors.[14,16,17] Protocol-defined dose reductions were based on clinical observations and did not define the offending agent, so dose reductions of VCR for neuropathy could not address the potential contribution of other agents. While our study shows that modest dose reductions do not affect OS, we were unable to measure chronic side effects of therapy. Therefore, we cannot evaluate whether these dose reductions led to decreased side effects or long-term complications.

It is also important to note that while no statistically significant differences in OS and EFS were found between patients with and without a moderate decrease in VCR and

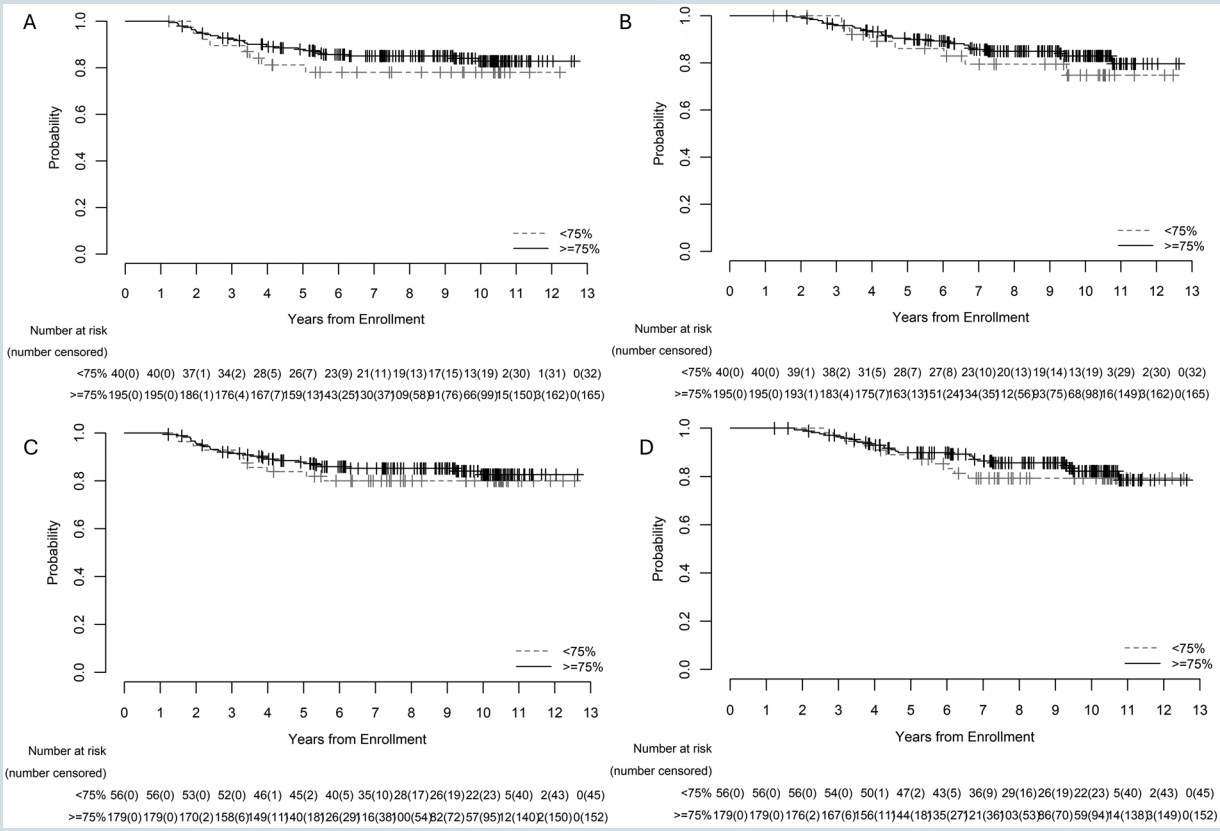

Figure 2. Survival curves for vincristine and cisplatin dose intensity received (<75% vs ≥75%): (A) EFS by percent vincristine ($P = .36$), (B) OS by percent vincristine ($P = .35$), (C) EFS by percent cisplatin ($P = .49$), and (D) OS by percent cisplatin ($P = .52$). Abbreviations: EFS, event-free survival; OS, overall survival.

Table 3. Event-free survival (EFS) by chemotherapy dose and medulloblastoma group.

	SHH			WNT			G3			G4		
	n	5-year EFS estimate (%) (SE)	*P*-value	*n*	5-year EFS estimate (SE)	*P*-value	*n*	5-year EFS estimate (SE)	*P*-value	*n*	5-year EFS estimate (SE)	*P*-value
Vincristine dose group												
<75%	6	83.3 (15.2)	.79	7	100.0 (0.0)	.66	4	50.0 (25.0)	.24	23	80.9 (8.6)	.23
≥75%	35	82.7 (6.5)		37	97.2 (2.7)		37	77.9 (6.9)		86	90.6 (3.2)	
Cisplatin dose group												
<75%	9	64.8 (16.5)	.33	3	100.0 (0.0)	.78	10	70.0 (14.5)	.37	34	91.2 (4.9)	.41
≥75%	32	87.4 (5.9)		41	97.5 (2.5)		31	76.8 (7.7)		75	87.6 (3.9)	

cisplatin dose intensity, a small difference may still exist. Examination of OS and EFS plots suggest that decreased dose intensity may have resulted in a small survival deficit, which was not shown in Nageswara Rao's prior analysis. While not statistically significant, the largest difference was seen in 5-year EFS in group 3 patients with decreased VCR dose. Differences were also noted in 5-year EFS of SHH tumors that received variable cisplatin dose and group 4 tumors that received variable VCR dose. In addition, other subgroup-dependent molecular biomarkers with prognostic significance (eg, MYC status in group 3 tumors, p53 status in SHH tumors) were not accounted for in this analysis. In a disease where every effort is made to maximize survival, this highlights that the risk of impaired survival through further dose reduction may not be tolerable especially in these higher risk medulloblastoma groups. Indeed, the most current COG study (ACNS2031) seeks to improve hearing outcomes not by reducing the dose of cisplatin but by

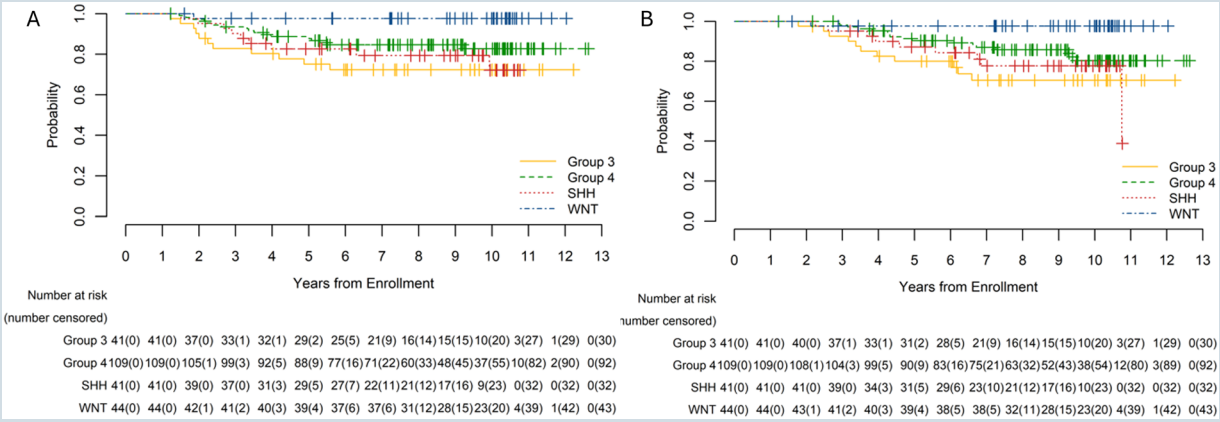

Figure 3. Survival curves by molecular subgroup across all patients ($n=235$). (A) EFS for the 4 molecular subgroups ($P=.012$) and (B) OS by molecular subgroup ($P=.008$). Molecular subgroup is a statistically significant predictor of overall survival in the total patient population. Abbreviations: EFS, event-free survival; OS, overall survival.

adding the otoprotective agent sodium thiosulfate (STS) for AR patients.

Our study is limited by its retrospective nature and was not powered to evaluate the impact of cumulative chemotherapy dose on survival. However, our large and well-characterized cohort enhances the reliability of our findings. Chemotherapy dose modification criteria were described comprehensively in the study protocol, minimizing the likelihood that reductions were driven by individual provider perceptions of patient risk. We examined demographic and tumor characteristics associated with dose reductions to further assess potential confounders. Older age was associated with VCR dose reduction (see Supplementary Table S3), which may reflect the higher incidence of VCR-induced neuropathy in older children.[31] Other potential confounding variables, such as pharmacogenomics, social determinants of health, and timing or reason for dose modification were not able to be evaluated in this analysis. Patients who experienced cisplatin dose reductions differed by molecular subgroups; 61% of all patients receiving cisplatin dose reductions were diagnosed with group 4 medulloblastoma compared to 5% diagnosed with WNT medulloblastoma. Although the poorer prognosis of group 4 medulloblastoma compared to WNT medulloblastoma was not fully appreciated during the time this study was conducted, these findings still suggest that dose reductions were not primarily driven by perceived risk or prognosis.

Advances in risk stratification of pediatric medulloblastoma have enabled personalized treatment strategies and improved survival outcomes.[1] Within these groups and risk stratifications, careful dose adjustments and the use of oto-protective agents like STS may help mitigate the severe side effects associated with higher cumulative doses of chemotherapy.[28] Ongoing studies of pediatric medulloblastoma are now examining the effect of dose reduction or other strategies to mitigate long-term toxicities (ACNS1422, ACNS2031) and may help to prospectively evaluate the impact of dose reductions on survival and toxicity.

Conclusion

Our study supports that moderate reductions in VCR and cisplatin dose intensity do not significantly affect survival in AR medulloblastoma. The effect of larger dose reductions or dose reductions in higher risk disease is unknown. Future research should focus on optimizing chemotherapy regimens to minimize long-term complications while maintaining efficacy, particularly in risk groups with favorable prognoses.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (https://academic.oup.com/neuro-oncology).

Keywords

average-risk medulloblastoma | cisplatin | vincristine

Author Contributions

All of the authors were involved in the conception and design of the project including data analysis and interpretation. In addition, all authors were involved in drafting, reviewing, and approval of the manuscript in its current submitted form. All authors agree to the integrity of the manuscript as presented. Initial concept design and data analysis: E.W., S.R., R.S., P.d.B., C.B., Y.L. Initial draft: E.W., S.R., P.d.B. Primary draft review and edits: E.W., S.R., R.S., P.d.B., Y.L., C.B., J.M.M., and A.J. Revisions: E.W., P.d.B., R.S., S.R., Y.L., C.B., J.M.M, and A.J.

Conflict of Interest Statement

No authors have any conflicts of interest to report. This content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Ethics Statement

Formal IRB review determined this project as not human subjects research and waived need for consent as this is a retrospective analysis of previously collected and deidentified data.

Data Availability

The Children's Oncology Group Data Sharing policy describes the release and use of COG individual subject data for use in research projects in accordance with National Clinical Trials Network (NCTN) Program and NCI Community Oncology Research Program (NCORP) Guidelines. Only data expressly released from the oversight of the relevant COG Data and Safety Monitoring Committee (DSMC) are available to be shared. Data sharing will ordinarily be considered only after the primary study manuscript is accepted for publication. For phase 3 studies, individual-level deidentified datasets that would be sufficient to reproduce results provided in a publication containing the primary study analysis can be requested from the NCTN/NCORP Data Archive at https://nctn-data-archive.nci.nih.gov/. Data are available to researchers who wish to analyze the data in secondary studies to enhance the public health benefit of the original work and agree to the terms and conditions of use. For nonphase 3 studies, data are available following the primary publication. An individual-level deidentified dataset containing the variables analyzed in the primary results paper can be expected to be available upon request. Requests for access to COG protocol research data should be sent to: datarequest@childrensoncologygroup.org. Data are available to researchers whose proposed analysis is found by COG to be feasible and of scientific merit and who agree to the terms and conditions of use. For all requests, no other study documents, including the protocol, will be made available and no end date exists for requests. In addition to above, release of data collected in a clinical trial conducted under a binding collaborative agreement between COG or the NCI Cancer Therapy Evaluation Program (CTEP) and a pharmaceutical/biotechnology company must comply with the data sharing terms of the binding collaborative/contractual agreement and must receive the proper approvals.

Affiliations

Department of Hematology-Oncology, Akron Children's Hospital, Akron, Ohio (E.W., S.R.); Department of Biostatistics, St. Jude Children's Research Hospital, Memphis, Tennessee (C.B., Y.L.); Department of Pediatrics, Emory School of Medicine, Atlanta, Georgia (A.J.); Department of Radiation Oncology, Washington University School of Medicine, St. Louis, Missouri (J.M.M.); Department of Hematology-Oncology, Boston Children's Hospital/Dana Farber Cancer Institute, Boston, Massachusetts (R.S.); Department of Oncology, University of Cincinnati School of Medicine and Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio (P.d.B.)

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