Evaluation of amifostine for protection against cisplatin-induced serious hearing loss in children treated for average-risk or high-risk medulloblastoma


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Background. The purpose of this study was to evaluate amifostine for protection from cisplatin-induced serious hearing loss in patients with average-risk medulloblastoma by extending a previous analysis to a much larger sample size. In addition, this study aimed to assess amifostine with serious hearing loss in patients with high-risk medulloblastoma treated with cisplatin.

Methods. Newly diagnosed medulloblastoma patients (n = 379; ages 3 – 21 years), enrolled on one of 2 sequential St. Jude clinical protocols that included 4 courses of 75 mg/m2 cisplatin, were compared for hearing loss by whether or not they received 600 mg/m2 of amifostine immediately before and 3 hours into each cisplatin infusion. Amifostine administration was not randomized. The last audiological evaluation between 5.5 and 24.5 months following protocol treatment initiation was graded using the Chang Ototoxicity Scale. A grade of ≥2b (loss requiring a hearing aid or deafness) was considered a serious event.

Results. Among average-risk patients (n = 263), amifostine was associated with protection from serious hearing loss (adjusted OR, 0.30; 95% CI, 0.14 – 0.64). However, there was insufficient evidence to conclude that amifostine prevented serious hearing loss (OR, 0.89; 95% CI, 0.31 – 2.54).

Conclusions. Although patients in this study were not randomly assigned to amifostine treatment, we found evidence in favor of amifostine administration for protection against cisplatin-induced serious hearing loss in average-risk but not in high-risk, medulloblastoma patients.

Keywords: audiology, brain neoplasms, late effects, ototoxicity, platinum drugs.

Cisplatin is a platinum-based chemotherapeutic agent used in frontline treatment regimens for a variety of brain and other solid tumors of childhood including average-risk and high-risk medulloblastoma.1,2 Unfortunately, cisplatin is a potent ototoxic. Cisplatin and other platinum-based chemotherapeutic agents cause cochlear (sensory) hair cell destruction, initially at the base...
of the cochlea where high frequency sounds are processed, and then progressing to the lower frequency sounds (and speech ranges) with increasing cumulative doses. Cisplatin treatment results in a high proportion of patients with permanent bilateral sensorineural hearing loss, with young children being more susceptible than older children. Approximately 50% of childhood medulloblastoma occurs before age 5 years and 80% before age 10 years; thus, cisplatin-induced hearing loss is often experienced during critical stages of speech and language acquisition and development. Considering that the combined effects of other treatments, namely surgery and craniospinal irradiation, result in neurocognitive deficits, it follows that the added insult of sensorineural hearing loss can be a significant detriment to the long term academic and social well-being of the surviving child.

Currently, no established treatments or procedures exist to prevent platinum-induced hearing loss in children or adults. Amifostine, a prodrug metabolized in humans to WR-1065, is a thiol-reducing agent and potent free-radical scavenger with demonstrated otoprotective properties against cisplatin in experiments using hamsters and guinea pigs. Evaluation of amifostine as a cisplatin otoprotectant in childhood cancer treatment has been limited to small studies with results suggesting no positive effect. In contrast, we previously reported protection against cisplatin-induced ototoxicity from amifostine in 62 average-risk, newly diagnosed medulloblastoma participants treated in 2 consecutive multi-institutional medulloblastoma clinical trials (SJMB96 and SJMB03), compared with 35 medulloblastoma participants treated with the same cisplatin dosing schedule on SJMB96 who did not receive amifostine. Among the non-amifostine-treated participants, 37% had serious ototoxicity (hearing loss requiring hearing aids or resulting in deafness), while only 14.5% of the amifostine-treated participants experienced serious ototoxicity (P = .005). We present here an extended analysis of amifostine in average-risk medulloblastoma patients using a much larger patient base now available (n = 263) and examine for the first time the potential benefit of amifostine in children being treated for high-risk medulloblastoma (n = 116).

**Materials and Methods**

**Patients**

Patients with average-risk or high-risk newly diagnosed medulloblastoma were enrolled on one of 2 successive clinical trial protocols, SJMB96 or SJMB03, at St. Jude Children's Research Hospital or at one of 9 collaborating institutions. The SJMB96 protocol was amended towards the end of the recruitment period to include amifostine administration for protection against ototoxicity, although no randomization was employed. Both study protocols were approved by the Human Subjects Institutional Review Boards at St. Jude Children’s Research Hospital and each of the participating institutions. Eligibility criteria and treatment regimens were previously described. Eligibility for inclusion in this analysis included diagnosis of medulloblastoma between September 1996 and March 2012, age at diagnosis of at least 3 years, and at least one audiological examination between 5.5 and 24.5 months after protocol treatment initiation. Patients with nontansient hearing loss in at least one ear at baseline were excluded, as were patients who did not receive cisplatin.

**Treatment Protocol**

After resection, participants on SJMB96 and SJMB03 were classified as having average-risk medulloblastoma (≤1.5 cm³ residual tumor and no metastatic disease) or high-risk medulloblastoma (>1.5 cm³ residual disease and/or metastatic disease localized to the neuroaxis) according to a modified Chang staging system. Participants with high-risk medulloblastoma were treated using craniospinal irradiation (MO-1, 36 Gy; M2-3, 36–39.6 Gy) and supplemental (“boost”) irradiation to the tumor bed using conformal treatment methods (total dose 55.8 Gy). When appropriate, local sites of metastasis received supplemental irradiation (total dose 50.4–54 Gy). Participants with average-risk medulloblastoma received 23.4 Gy craniospinal irradiation and supplemental irradiation to the posterior fossa (cumulative dose 36 Gy) and tumor bed (total dose 55.8 Gy; 2 cm margin). On the SJMB03 protocol, supplemental irradiation of the posterior fossa was eliminated for average-risk participants, and the clinical target volume to the tumor bed was reduced from 2.0 cm (SJMB96 protocol) to 1.0 cm for all patients. Following radiation therapy, at ~12 weeks post-treatment initiation, all participants (both protocols) received 4 cycles of cyclophosphamide, vincristine, cisplatin, and stem cell or bone marrow rescue. Each cycle was 28 days in duration, and the cisplatin dose level was 75 mg/m², to a cumulative prescribed dose of 300 mg/m².

**Amifostine Administration**

Based on the pharmacokinetic disposition of amifostine and its active metabolite WR1065, we chose to administer amifostine at a dosage of 600 mg/m² as a 1 minute intravenous infusion immediately preceding and again 3 hours into each of the 4 courses of cisplatin infusion. The supportive care guidelines followed for amifostine administration have been previously described and included prehydration, withholding hypertension medication 24 hours before treatment and performing blood pressure control procedures, and close monitoring of and corrective measures for calcium level.

**Audiological Methods**

Audiological evaluations, with method dependent upon participant age, cognition, development, and cooperation, included conventional pure-tone audiometry, conditioned play audiometry, visual reinforcement audiometry, speech audiometry, tympanometry, distortion product otoacoustic emissions (DPOAEs), auditory brainstem response (ABR), and/or auditory steady-state response (ASSR). Otoscopy and tympanometry were performed on each participant to assess the integrity of the outer, middle, and middle ear spaces. Air conduction thresholds were measured in a sound-treated booth at 0.25, 0.50, 1, 2, 4, 6, and 8 kHz to determine hearing sensitivity in decibels (dBs) hearing level. Bone conduction thresholds were obtained at 0.25, 0.50, 1, 2, 3, 4, 6 kHz in dBs hearing level, as needed to determine the nature of the hearing impairment. Although conventional audiometry remains the standard for ototoxicity monitoring, more objective diagnostic measurements were required for a small number of participants. Click and tone-burst ABR, ASSR, and/or DPOAEs were performed on participants who were unable to respond to conventional audiometric techniques (eg, young age or developmental delay). ABR and ASSR evaluations were performed to estimate peripheral hearing sensitivity at frequencies 0.50, 1, 2, 4, and 8 kHz. DPOAEs were evaluated to determine cochlear outer hair cell function at frequencies 1–8 kHz. Of the total number of evaluable participants, 18 (5%) received an ABR/ASSR evaluation at baseline with subsequent conventional audiometric evaluations; 7 (2%) had DPOAEs performed for the baseline evaluation with subsequent conventional audiometric evaluations, and 5 (1%) received an ABR/ASSR evaluation at baseline and throughout treatment. Audiological procedures were completed by a certified audiologist at each of the 10 collaborative study sites. Every audiological evaluation was reviewed and assigned an ototoxicity grade by a clinical research audiologist (JB) at St. Jude Children's Research Hospital. The prospective ototoxicity monitoring protocol consisted of an evaluation at the following time points: baseline (occurred within 2 weeks of initiation of radiation therapy), before each of the 4 high-dose cisplatin
chemotherapy cycles, and at 3, 6, 9, 18, and 24 months after completion of
treatment. In our previous amifostine evaluation,17 the ototoxicity grading
criteria were based on a Children's Cancer Group method with grade 3
defined as > 25 dB hearing loss at 2000 Hz and grade 4 as ≥ 40 dB loss at
2000 Hz.20 In our present study, ototoxicity grade for each audiologial
examination in each ear was based on the more contemporary Chang Ototox-
icty Scale (Table 1).21 Similar to our previous study, serious hearing loss for
this analysis was defined as deafness or loss requiring a hearing aid, which
corresponds to Chang grades 2b, 3, or 4.22 For asymmetrical hearing loss,
the child's worse ear grade was used for the analysis.

Statistical Approach
Chi-square exact tests were used to examine the association between the
distribution of Chang grade and amifostine treatment status. Univariable
and multivariable logistic regression methods were used to study associa-
tions between dichotomized ototoxicity outcomes and a predetermined
set of covariates. In building multivariable logistic regression models,
a backwards selection approach was employed where goodness of fit
across candidate models was compared via Akaike and Bayesian informa-
tion criteria. All P values were based on 2-sided tests and were not adjusted
for multiplicity.

Results
Patient Participation
Of 452 participants with medulloblastoma who were enrolled in
SJMB96 or SJMB03 through March 2012, 418 had at least one audi-
ology examination during the eligible time period (5.5 to 24.5
months postprotocol treatment initiation, [ie, 1.5–21.5 months
post initiation of cisplatin treatment]). Of these, 35 were not eligible
due to nontransient hearing loss at baseline in at least
one ear, and 4 more were excluded because they did not receive
cisplatin or had no cisplatin information available. Thus, 379 partici-
pants were included in the analysis (Fig. 1).

Participant Characteristics by Amifostine Status
Table 2 provides selected characteristics of participating patients
by amifostine treatment status. Distributions of sex, race, and
disease risk level were similar between the 2 groups, as was
median cumulative cisplatin dose (~ 300 mg/m² in both groups).
Median months from treatment initiation to last hearing evalu-
ation was 19.5 in the amifostine-treated group, compared with
18.9 in the nontreated group. Of the 51 participants who did not
receive amifostine and thus served as the referent (control)
group for the analysis, 34 (67%) were classified as average risk
and 17 as high risk. For those who received amifostine, 229
(70%) had average-risk tumors, and 99 had high-risk tumors.

Hearing Loss by Amifostine Treatment Status
Some degree of hearing loss (Chang grade ≥ 1a) was evident in
67% of participants. Fig. 2 provides cumulative incidence curves,
plootted as proportions, from treatment initiation to first audiologic
evaluation with evidence of (i) any hearing loss and (ii) serious
hearing loss (Chang grade ≥ 2b). The curves illustrate that
hearing loss occurred shortly after cisplatin initiation and plat-
eaued by 9 months. As shown in Table 3, the distribution by
Chang grade, not accounting for disease risk category, showed a
clear tendency toward worse hearing level among the 51 partici-
ants who did not receive amifostine, relative to the 328 partici-
ants who received amifostine treatment (P = .05, chi-square
exact test). Serious hearing loss was evident in 53% of participants
who did not receive amifostine compared with 32% of participants
who were treated with amifostine (P = .004; univariable logistic re-
gression model). As noted in Table 3 based on univariable models,
younger age at diagnosis, male sex, and high-risk disease were also
found to be associated with significant hearing loss. Being treated
on SJMB03 and larger cumulative doses of cisplatin were asso-
ciated with lower risk of significant ototoxicity. As per protocol,
cisplatin treatment was discontinued for participants who experi-
enced significant hearing loss, which explains the latter result.
Based on a multivariable model, the odds ratio for the effect of ami-
foistine on Chang grade ≥ 2b (vs < 2b) adjusted for disease risk cat-
egory, age at diagnosis, and sex, was 0.43 (95% CI, 0.23–0.80),
suggesting a strong reduction in risk for serious hearing loss
among participants treated with amifostine in this study (detailed
results of this model are in Supplementary Table 1). Note that
because the craniospinal radiation dose was determined by
disease risk and there was very little deviation from the prescribed
dose, radiation dose was accounted for in these analyses by way of
disease risk. We chose to incorporate disease risk rather than cra-
niospinal radiation dose into our models for ease of interpretation.

Hearing Loss by Disease Risk and Amifostine Treatment
Status
Table 4 provides data on the distribution of hearing levels stratified
by disease risk category and amifostine treatment status. Overall, a
larger proportion of participants with high-risk medulloblastoma
suffered some degree of hearing loss (76%) than did the
average-risk participants (62%, P = .01, chi-square exact test),
and the distribution was weighted toward more severe loss in the
high-risk participants. For average-risk participants, hearing level
was significantly worse among those not treated with amifostine
compared with participants who received amifostine treatment
(P = .01, chi-square exact test). In contrast, the overall distribution
by Chang grade did not differ statistically in the high-risk disease
group by amifostine treatment status (P = .93). The moderated
effect of amifostine by disease risk on Chang grade ≥ 2b hearing
loss is further illustrated in Table 3 and in Supplementary Fig. 1.
The right half of Table 3 summarizes the results of the multivariable
logistic regression analysis. After adjustment for age at diagnosis
and sex, and incorporating disease risk-amifostine interaction,
Amifostine appeared to provide a strong protective benefit against cisplatin-induced serious hearing loss in average-risk participants (adjusted OR, 0.30 [95% CI, 0.14–0.64]), but not for high-risk participants (adjusted OR, 0.89 [95% CI, 0.31–2.54]).

Discussion

In this study of 379 newly diagnosed childhood medulloblastoma participants, we confirmed an earlier result from our multi-institutional study that amifostine, administered at 600 mg/m² both immediately before and again 3 hours into each of four 75 mg/m² cisplatin infusions provides protection from cisplatin-induced sensorineural hearing loss. Here we extend the previous finding using a much larger sample size and show that the otoprotective effect of amifostine in average-risk participants (adjusted OR, 0.30 [95% CI, 0.14–0.64]) was not present in high-risk participants (adjusted OR, 0.89 [95% CI, 0.31–2.54]). Given that the cisplatin and amifostine dosing schedules were identical between the

Fig. 1. Flow diagram of study participation.
Table 2. Characteristics of 379 medulloblastoma participants by amifostine treatment status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Amifostine = No (n = 51)</th>
<th>Amifostine = Yes (n = 328)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at study enrollment (years)</td>
<td>7.3 (3.2, 17.2)</td>
<td>8.3 (3.1, 21.6)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>18 (35.3%)</td>
<td>118 (36.0%)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>33 (64.7%)</td>
<td>210 (64.0%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-white (%)</td>
<td>13 (25.5%)</td>
<td>73 (22.3%)</td>
</tr>
<tr>
<td>White</td>
<td>38 (74.5%)</td>
<td>255 (77.7%)</td>
</tr>
<tr>
<td>Institution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>St. Jude</td>
<td>27 (52.9%)</td>
<td>165 (50.3%)</td>
</tr>
<tr>
<td>Collaborative institution</td>
<td>24 (47.1%)</td>
<td>163 (49.7%)</td>
</tr>
<tr>
<td>Cumulative cisplatin dosage (mg/m²) [median (min, max)]</td>
<td>301.0 (76.8, 329.4)</td>
<td>299.8 (74.5, 312.2)</td>
</tr>
<tr>
<td>Time from treatment initiation to latest audiogram (months) [median (min, max)]</td>
<td>18.9 (6.3, 24.3)</td>
<td>19.5 (5.6, 24.5)</td>
</tr>
<tr>
<td>Study protocol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SJMB03</td>
<td>3 (5.9%)</td>
<td>263 (80.2%)</td>
</tr>
<tr>
<td>SJMB96</td>
<td>48 (94.1%)</td>
<td>65 (19.8%)</td>
</tr>
<tr>
<td>Disease risk category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>34 (66.7%)</td>
<td>229 (69.8%)</td>
</tr>
<tr>
<td>High</td>
<td>17 (33.3%)</td>
<td>99 (30.2%)</td>
</tr>
<tr>
<td>Chang Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>9 (17.7%)</td>
<td>118 (36.0%)</td>
</tr>
<tr>
<td>1a</td>
<td>9 (17.7%)</td>
<td>60 (18.3%)</td>
</tr>
<tr>
<td>1b</td>
<td>4 (7.8%)</td>
<td>24 (7.3%)</td>
</tr>
<tr>
<td>2a</td>
<td>2 (3.9%)</td>
<td>22 (6.7%)</td>
</tr>
<tr>
<td>2b</td>
<td>5 (9.8%)</td>
<td>19 (5.8%)</td>
</tr>
<tr>
<td>3</td>
<td>18 (35.3%)</td>
<td>77 (23.5%)</td>
</tr>
<tr>
<td>4</td>
<td>4 (7.8%)</td>
<td>8 (2.4%)</td>
</tr>
</tbody>
</table>

Abbreviation: St. Jude, St. Jude Children’s Research Hospital.

Amifostine was previously evaluated for protection against cisplatin-induced hearing loss in children in 2 randomized clinical trials, as reviewed in detail by van As et al. Gallegos-Castorena et al. randomized 28 children with osteosarcoma to no amifostine (n = 13) or amifostine (n = 15; 740 mg/m²) prior to cisplatin infusions of 150 mg/m². None of the participants in either the amifostine group or the control group had grade 3 or 4 ototoxicity, and there was no statistical difference in the overall distribution of ototoxicity grade between the 2 groups, although the sample size was quite small. Katzenstein et al. in a Children’s Oncology Group randomized trial of 82 evaluable participants with hepatoblastoma, compared amifostine (740 mg/m² 15 min before each cycle of 100 mg/m² cisplatin or 3 mg/m² cisplatin if younger than 1 year; n = 37) with no otoprotective agent (n = 45) in an unplanned interim analysis unrelated to ototoxicity. In both treatment arms, the incidence of significant hearing loss (≥ 40 dB at 3–5 kHz or worse) was 38%. In a nonrandomized study, Marina et al. evaluated amifostine in 25 pediatric germ cell tumors. That study administered intravenous amifostine at 825 mg/m² over 15 minutes, 30 minutes before cisplatin infusion of 40 mg/m² per day for 5 consecutive days for each cycle. They reported that 18 of 24 (75%) evaluable participants had grade 2–4 hearing loss using the Brock grading scale, similar in proportion to a historical comparison group from a previous extragonadal childhood germ cell study (41/55 with grade 2–4, 75%). Finally, Fisher et al. administered amifostine at 1000 mg/m² prior to and 4 hours into each cisplatin infusion of 70 mg/m² in 11 children undergoing treatment for medulloblastoma or supratentorial PNET. In audiological evaluations conducted at 1–3 years post treatment, 4 of the 11 participants had hearing loss severe enough to require hearing aids and 3 others had grade 2 hearing loss. Although clearly limited by sample size and study design issues, none of these studies provided evidence in support of amifostine for cisplatin-induced ototoxicity among pediatric solid tumor patients.

Sodium thiosulfate, an alternative to amifostine, is currently being tested in clinical trials for otoprotection in solid tumor treatment through the Children’s Oncology Group ACCL0431 protocol and for hepatoblastoma treatment in the International Society of Pediatric Oncology SIOPEL-6 protocol. Results have not been published from either of these trials to date. Sodium thiosulfate, like amifostine, is a thiol-reducing agent with strong antioxidant properties and is reported to be easier to administer than amifostine and have less potential for clinically significant adverse effects. Of the 263 participants in SJMB03 who received amifostine in our study, 25 (9.5%) experienced grade 3 or 4 toxicity secondary to amifostine: 3 with a grade 3 allergic reaction; 19 with grade 3 hypotension; and 2 with grade 4 hypotension.

Considerations for interpreting our results include the fact that we did not randomize participants to amifostine or no amifostine treatment, and the non-amifostine-treated group used for comparison purposes was largely accrued in the early stages of the SJMB96 study. We also did not have systematic data available on cochlear radiation doses, although, as we previously reported, no difference in mean cochlear radiation dose was observed in a subgroup analysis of 56 participants that compared those with grade 3 ototoxicity to those with < grade 3 (mean cochlear dose of 49 Gy for each group). In addition, the time frame for audiologic follow-up in our study was defined by the latest examination that occurred between 5.5–24.5 months following protocol treatment initiation, potentially failing to capture delayed onset or further
deterioration of hearing loss. Although our data demonstrated that hearing loss stabilized at 9 months following initiation of protocol treatment, continued decline in hearing sensitivity years after therapy has been documented in patients treated with cisplatin.\textsuperscript{27,28} and cranial radiation.\textsuperscript{29,30}

The strengths of this research include the prospective and comprehensive audiological evaluations conducted and the standardized protocol used throughout the study period for administration of cisplatin, for effective supportive care for amifostine, and for administration of amifostine. In addition, the results of our published pharmacokinetic study of amifostine and WR1065 in this patient population further lead credence to the selection of the amifostine dosage and schedule for this patient population.\textsuperscript{10} We also used a standardized coding method, the Chang ototoxicity grading scale,\textsuperscript{21} to assess hearing level for all participants, which has notable advantages over the NCI CTCAE v3.0 method and other earlier ototoxicity scales\textsuperscript{3,20} including the scale used in our previous analysis.

In summary, in this large study of medulloblastoma patients treated with 300 mg/m\textsuperscript{2} cumulative dose cisplatin, amifostine provided clinically meaningful benefit for reducing serious cisplatin-induced hearing loss in participants treated for average-risk disease.

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**Table 3.** Univariable and multivariable logistic regression results for risk of serious hearing loss versus demographic and clinical covariates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable Logistic Regression Model</th>
<th>Multivariable Logistic Regression Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>Standard Error</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>-0.099</td>
<td>0.032</td>
</tr>
<tr>
<td>Race (white)</td>
<td>0.184</td>
<td>0.263</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>0.578</td>
<td>0.235</td>
</tr>
<tr>
<td>Cumulative cisplatin dose</td>
<td>-4.272</td>
<td>2.710</td>
</tr>
<tr>
<td>Study (SJMB03)</td>
<td>-0.917</td>
<td>0.232</td>
</tr>
<tr>
<td>Risk (high)</td>
<td>0.744</td>
<td>0.230</td>
</tr>
<tr>
<td>Amifostine (yes)</td>
<td>-0.885</td>
<td>0.305</td>
</tr>
<tr>
<td>Risk by amifostine interaction*</td>
<td>1.087</td>
<td>0.661</td>
</tr>
</tbody>
</table>

Amifostine vs no amifostine for average-risk disease

Amifostine vs no amifostine for high-risk disease

*Since the multivariable model contains a risk by amifostine interaction term, the odds ratio for amifostine versus no amifostine needs to be calculated by risk level, and odds ratios associated with the main effects (ie, risk alone or amifostine alone) are not meaningful.

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**Fig. 2.** Cumulative proportion of ototoxicity versus time from protocol treatment initiation.

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but not for participants treated for high-risk disease. As such, the new St. Jude medulloblastoma protocol (SJMB12), which opened at St. Jude Children’s Research Hospital in June 2013 and will include 19 collaborative sites across North America, Australia, and New Zealand, incorporates amifostine for patients with average-risk, but not high-risk, medulloblastoma using the dosing schedule described herein.

**Supplementary Material**

Supplementary material is available online at Neuro-Oncology (http://neuro-oncology.oxfordjournals.org/).

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**References**


