

# Delayed Sodium Thiosulfate as an Otoprotectant Against Carboplatin-induced Hearing Loss in Patients with Malignant Brain Tumors<sup>1</sup>

Nancy D. Doolittle, Leslie L. Muldoon,  
Robert E. Brummett, Rose Marie Tyson,  
Cynthia Lacy, Joseph S. Bubalo,  
Dale F. Kraemer, Michael C. Heinrich,  
James A. Henry, and Edward A. Neuwelt<sup>2</sup>

Departments of Neurology [N. D. D., L. L. M., R. M. T., C. L., E. A. N.], Pharmacology [R. E. B., J. S. B.], Otolaryngology [R. E. B.], Medicine [M. C. H.], Divisions of Medical Informatics and Outcomes Research [D. F. K.], Hematology and Medical Oncology [M. C. H.], Oregon Health Sciences University, and Research Service [E. A. N.], and Rehabilitation Research and Development Service, National Center for Rehabilitative Auditory Research [J. A. H.], Veterans Affairs Medical Center [M. C. H., J. A. H., E. A. N.], Portland, Oregon 97201

## ABSTRACT

Carboplatin is effective in the treatment of malignant brain tumors. However, when administered in conjunction with osmotic opening of the blood-brain barrier (BBB), carboplatin is ototoxic. The purpose of this study was to determine whether delayed administration of sodium thiosulfate (STS), given after BBB closure, provided protection against carboplatin ototoxicity. Patients underwent monthly treatment with intra-arterial carboplatin (200 mg/m<sup>2</sup>/day × 2) in conjunction with osmotic opening of the BBB, for up to 1 year. Audiological assessment was conducted at baseline and within 24 h before each monthly treatment. STS was administered i.v. as one (20 g/m<sup>2</sup>) or two (20 g/m<sup>2</sup> and 16 g/m<sup>2</sup>) 15-min doses, depending on baseline hearing status. The initial group received the first STS dose 2 h (or 2 and 6 h) after carboplatin (STS2) and a subsequent group received STS 4 h (or 4 and 8 h) after carboplatin (STS4). Audiological data were compared with a historical comparison group (HCG) treated with carboplatin without STS. Spearman correlation coefficients comparing STS 2 ( $n = 24$ ), STS4 ( $n = 17$ ), and HCG ( $n = 19$ ) indicated significantly lower rates of ototoxicity with increased delay in STS

( $P = 0.0006$ ). On the basis of the analysis of hearing levels, there were significant differences among the two STS groups and HCG at 8000 Hz ( $P = 0.0010$ ) and at 4000 Hz ( $P = 0.0075$ ). The log-rank test for time to ototoxicity indicated a significant difference between STS4 and HCG ( $P = 0.0018$ ). Delayed STS was effective in protecting against carboplatin-induced hearing loss. STS delayed to 4 h after carboplatin significantly decreased time to development of ototoxicity and rate of ototoxicity when compared with HCG.

## INTRODUCTION

Platinum chemotherapy agents have shown efficacy in both systemic and CNS<sup>3</sup> malignancies (1). Cisplatin [*cis*-diaminedichloroplatinum (II)] is an effective drug in head and neck (2, 3), lung (4–6), ovarian (7, 8), and testicular (9) cancer. Dose-limiting effects associated with cisplatin include severe renal, neurological, and auditory toxicity. Although cisplatin nephrotoxicity may be avoided with hydration and diuresis (4), ototoxicity remains an irreversible, dose-limiting side effect of this drug (10–16). The reported incidence of cisplatin-induced hearing loss ranges from 4–91% (17, 18).

Carboplatin [*cis*-diammine (1, 1-cyclobutane-dicarboxylato) platinum (II)], an analogue of cisplatin, was introduced in the early 1980s to help avoid some of the toxicities of cisplatin. It has been suggested that carboplatin is equivalent to cisplatin in the treatment of suboptimally debulked ovarian cancer, extensive-stage small cell lung cancer, and non-small cell lung cancer (4). Additionally, carboplatin is effective in the treatment of malignant brain tumors (19–21). The delivery of carboplatin-based therapy in conjunction with osmotic opening of the BBB has shown efficacy in single- (22, 23) as well as multi-institutional (24) studies, particularly in astrocytoma, PNET, germ cell tumor, and CNS metastases. Osmotic BBBD is induced by a 30-second i.a. infusion of 25% mannitol into a selected internal carotid or vertebral artery, depending on tumor location (25, 26). By transiently opening the BBB, this technique creates a two-compartment model, as well as providing the opportunity to increase chemotherapy delivery to the CNS (25).

Carboplatin-induced ototoxicity has been reported by several investigators (17, 22, 27–29). Parsons *et al.* (28) noted ototoxicity in 9 of 11 (82%) of children with neuroblastoma treated with autologous bone marrow transplantation when car-

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<sup>2</sup> To whom requests for reprints should be addressed, at Oregon Health Sciences University, 3181 SW Sam Jackson Park Road-L603, Portland, OR 97201-3098. Phone: (503) 494-5626; Fax: (503) 494-5627; E-mail: neuwelte@ohsu.edu.

<sup>3</sup> The abbreviations used are: CNS, central nervous system; i.a., intra-arterial; BBB, blood-brain barrier; BBBD, blood-brain barrier disruption; STS, sodium thiosulfate; PNET, primitive neuroectodermal tumor; HCG, historical comparison group; dB, decibel; HL, hearing level; ANCOVA, analysis of covariance; RICA, right internal carotid artery; SD, stable disease.

boplatin was part of their conditioning regimen. We reported ototoxicity when carboplatin was administered across an open BBB, particularly in the vertebral artery circulation (22, 27).

Hearing loss negatively affects quality of life. Children undergoing treatment with platinum chemotherapy are at risk for ototoxicity (28), which can delay development of language and reading skills (30). Studies in elderly individuals document depressive symptomatology in the hearing-impaired (31, 32). In an attempt to ameliorate this problem, several thiol-containing compounds have been studied for potential otoprotective activity against cisplatin. Although amifostine (33, 34) has shown efficacy in decreasing cisplatin-induced nephrotoxicity, its otoprotective effect is unclear. In animal models, D-methionine (10, 11) reduced the hearing loss caused by high-dose cisplatin, however this agent has not yet been tested in clinical trials. On the basis of encouraging results in animal models (35), we conducted a Phase I clinical study in 1996 to determine a safely tolerated dose of STS (American Regent Laboratories, Inc., Shirley, NY) and to obtain preliminary data on the otoprotective effect of STS against carboplatin-induced ototoxicity (27). Patients were treated with a two-route, two-compartment model. That is, carboplatin was administered i.a. within 5 min after osmotic opening of the BBB. Two h after carboplatin, when BBB permeability generally returned to baseline, creating two compartments, STS was administered i.v. The maximum tolerated dose of STS was 20 g/m<sup>2</sup> (27).

A key concern is the potential effect of STS on platinum efficacy against tumor. In CNS malignancies, the creation of a two-compartment model by BBBD, should minimize this effect through administration of STS after BBB closure. This two-compartment model and the high ratio of STS:carboplatin required to inactivate carboplatin (27, 35–37) suggest it is unlikely that STS interferes with the cytotoxic effects of CNS drug. However, in non-CNS malignancies, the effect of STS on platinum cytoreduction remains a problem. One alternative to avoid the negative interactions of platinum chemotherapeutics and STS is to delay the administration of STS. In laboratory studies of a nude rat model of human small cell carcinoma grown subcutaneously, delayed administration of STS (*e.g.*, to 8 h) did not impact the efficacy of carboplatin (38). The purpose of the present clinical study was to describe the differences in hearing protection in patients with malignant brain tumors when STS administration was delayed from 2 h to 4 h after carboplatin with BBB opening, compared with a HCG of patients treated with carboplatin with BBB opening who did not receive STS.

## MATERIALS AND METHODS

The study was approved by the Institutional Review Board of the Oregon Health Sciences University. Informed consent was obtained from each patient or from the patient's legal guardian, in accordance with institutional regulations.

**Audiological Assessment.** Patients generally underwent carboplatin treatment administered with osmotic opening of the BBB monthly on 2 consecutive days for up to 1 year. As patients entered the protocol, before treatment with carboplatin, they were required to undergo baseline audiological assessment. The assessment included air- and bone-conduction pure-tone thresholds of hearing sensitivity (250 to 8000 Hz). Patients underwent

audiograms monthly within 24 h before each treatment with carboplatin.

**Chemotherapy Regimen.** BBB opening was performed with the patient under general anesthesia as described previously (39). Depending on the location of the tumor, 25% mannitol was infused (5–10 ml/sec) into the appropriate internal carotid or vertebral artery, for 30 seconds. The combination chemotherapy regimen consisted of i.v. cyclophosphamide (330 mg/m<sup>2</sup>/day × 2 days; total dose, 660 mg/m<sup>2</sup>) beginning ~20 min before the mannitol infusion. Carboplatin (200 mg/m<sup>2</sup>/day × 2 days; total dose, 400 mg/m<sup>2</sup>) was infused i.a. over 10 min, starting within 5 min after the mannitol. Additionally, patients received either i.a. or i.v. etoposide phosphate (200 mg/m<sup>2</sup>/day × 2 days; total dose, 400 mg/m<sup>2</sup>).

**Dose and Timing of STS.** STS was available as a 25% (250 mg/ml) solution. Patient dose was determined (16 or 20 g/m<sup>2</sup>) and mixed with an equivalent amount of normal saline (1:1) for infusion. Because high-dose STS (16 or 20 g/m<sup>2</sup>) causes transient hypernatremia, hypertension, and controllable grade II nausea and vomiting (National Cancer Institute Common Toxicity Criteria, version 2.0), patients were premedicated with antiemetics before STS (27). The most commonly used antiemetic regimen consisted of benadryl (12.5 mg), dexamethasone (6 mg), and, if needed, ativan (0.5–1.0 mg), given i.v. 30–45 min before STS.

STS was administered i.v. over 15 min. Initially, patients were treated with one dose of STS 2 h after carboplatin (27). Because 50% of patients with impaired baseline hearing developed an additional 20-dB threshold shift, it was clear that one dose of STS was insufficient to prevent ototoxicity (40) in these patients. Therefore, in August 1997, patients with good to excellent baseline hearing sensitivity (thresholds <20 dB HL at all frequencies within the range of 250–8000 Hz) continued to receive one dose of STS (20 g/m<sup>2</sup>) 2 h after carboplatin. Patients with impaired baseline hearing (thresholds >20 dB HL at one frequency and/or >15 dB HL at two consecutive frequencies, within the range of 250–8000 Hz) received one dose of STS (20 g/m<sup>2</sup>) 2 h after carboplatin and a second dose (16 g/m<sup>2</sup>) 6 h after carboplatin. Patients with good to excellent baseline hearing who sustained an ototoxic shift (≥20 dB threshold shift at any frequency, ≥10 dB shift at two adjacent test frequencies, or loss of response at three consecutive test frequencies where responses were obtained at baseline; Ref. 40) during the year-long carboplatin treatment thereafter received the two-dose STS regimen.

Through March 1998, patients received the first STS dose 2 h after carboplatin. In April 1998, after discussions with several investigators using osmotic opening of the BBB to treat patients with malignant brain tumors, the decision was made to allow a greater delay between opening the BBB and administering STS. The reason for this decision was data suggesting a greater time of increased barrier permeability after osmotic opening than was previously thought (26). Thereafter, administration of STS was delayed to 4 h after carboplatin. Patients with good to excellent baseline hearing received one dose of STS 4 h after carboplatin. Patients with impaired baseline hearing and patients who sustained an ototoxic shift during treatment (40) received the first dose of STS 4 h after carboplatin and the second dose of STS 8 h after carboplatin. The extended time

appeared justified based on data from our animal model suggesting that STS would minimize ototoxicity even when administered 8 h or more after carboplatin (38).

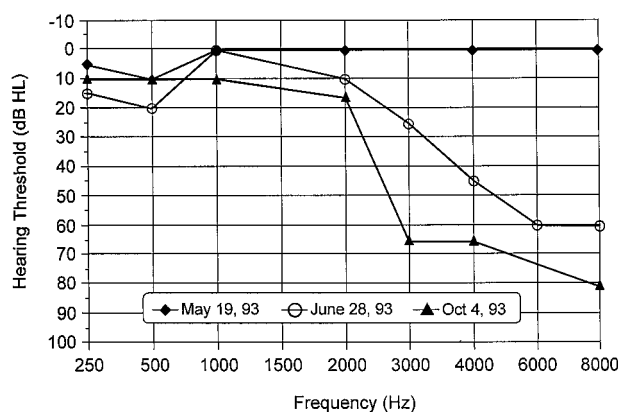
**Data Analysis.** Audiological data collected through mid-August 1999 were included in the statistical analysis. Data were analyzed in three treatment groups: the HCG, patients treated with STS at 2 (or 2 and 6) h after carboplatin (STS2), and patients treated with STS at 4 (or 4 and 8) h after carboplatin (STS4). For patients who changed from the 2-h to the 4-h STS protocol midway through the year-long carboplatin treatment, audiological data obtained during treatment with the 2-h STS protocol were included in STS2. Audiological data obtained after patients changed to the 4-h STS protocol were not included in the statistical analysis.

Two patients with impaired baseline hearing treated with the 2-h STS protocol were initially treated with one dose of STS but subsequently received two doses of STS. Because the first dose of STS was administered at 2 h, for the purposes of analysis these two patients were included in the STS2 group. Additionally, two patients were treated with one course of the 2-h STS protocol but subsequently, for the remainder of their carboplatin treatments, received the 4-h STS protocol. For the purposes of analysis, these two patients were included in the STS4 group.

Hearing levels were compared using a repeated-measures ANCOVA model. Baseline hearing levels and treatment number were fit as continuous variables, whereas treatment group and ear and audiometric test frequency were fit as factors. Various interactions among the factors and between factors and the continuous variables were also fit. A mixed-model approach (41) was used to perform these analyses. Three different correlation structures (autoregressive moving average, first-order autoregressive, and compound symmetry) were fit in each case, and the best model was selected using Akaike's information criterion. Because the full ANCOVA model included several significant interactions involving frequency, separate models (that is, frequency-specific models) were fit to better assess the associations in the full ANCOVA model. Least-squares means allow comparisons among mean values adjusted for other factors in a model. Comparisons among least-squares means are made with Tukey-Kramer adjustments for multiple comparisons. All analyses were performed using version 7.0 of SAS for Windows 95 (42).

As discussed in the results, frequency-specific ANCOVA models were also fit to these data. To maintain the overall significance level at the nominal level of 0.05, the *P* for these frequency-specific models should be compared with a Bonferroni-adjusted (43) significance level of 0.0083 (0.05 divided by 6, the number of test frequencies).

The number of treatments until ototoxicity occurred was estimated using Kaplan-Meier estimation, and these values were plotted as a function of treatment number. The log-rank test was used to compare the distributions of time with ototoxicity among the three treatment groups (44). Because a significant difference among the three groups did not specify which pairs of treatment groups are different, pairwise comparisons among the three treatment groups (with Bonferroni-adjusted significance level of 0.0167 for three pairs of comparisons) were run as



*Fig. 1* Patient audiogram showing hearing loss after carboplatin administered in conjunction with osmotic opening of the BBB in a representative patient in the HCG who did not receive STS. The baseline audiogram (May 19, 1993) from the right ear obtained before initiating carboplatin treatment and subsequent audiograms obtained after initiating carboplatin treatment (June 28, 1993 and October 4, 1993) are shown.

needed. A Spearman rank correlation (43) was computed to compare ototoxicity with the ordered treatment groups (HCG, STS2, and STS4).

## RESULTS

**HCG.** Between February 1992 and May 1995, 37 patients underwent treatment with carboplatin in conjunction with osmotic opening of the BBB before initiation of the Phase I clinical STS study. Patients in this cohort who received furosemide or other ototoxic agents, such as aminoglycoside antibiotics, were removed from the analysis; thus the historical comparison group included 19 patients, as reported previously (27). These patients underwent a total of 271 carboplatin treatments with 96 infusions in the vertebral arteries. Fig. 1 shows the decline in hearing in a representative patient in the HCG after treatment with BBBD plus carboplatin. This audiogram is an example of the hearing loss noted in the historical group, before initiation of the Phase I study. Fifty-three percent (10 of 19) of the patients in the historical group suffered ototoxicity after only one carboplatin treatment. The average loss in pure tone sensitivity was 20.8 dB  $\pm$  5.9 dB at 8000 Hz ( $n = 19$ ) after one treatment with carboplatin.

**STS Treatment Groups.** Forty-one patients were treated with high-dose STS in conjunction with 454 carboplatin treatments. Patient characteristics are listed in Table 1. Eleven (46%) of the patients in STS2 and four (24%) of the patients in STS4 had a history of radiation treatment that occurred before the determination of baseline hearing sensitivity thresholds for this study. Twenty-four patients were treated with the 2- (or 2- and 6-) h STS protocol (STS2). This group underwent 271 carboplatin treatments with 84 infusions in the vertebral arteries. Seventeen patients were treated with the 4- (or 4- and 8-) h STS protocol (STS4) and underwent 183 carboplatin treatments with 47 infusions in the vertebral arteries. Table 2 shows the number of patients in the HCG, STS2, and STS4 groups at each monthly

Table 1 Patient characteristics

	HCG	STS2	STS4
	No. of patients (%)	No. of patients (%)	No. of patients (%)
Total patients	19	24	17
Sex			
Male	11 (58)	11 (46)	7 (41)
Female	8 (42)	13 (54)	10 (59)
Prior treatment			
Chemotherapy	7 (37)	9 (38)	10 (59)
Radiotherapy	5 (21)	11 (46)	4 (24)
Age (yr)			
Median	30	43.5	44
Minimum	8	11	4
Maximum	67	66	63
No. of patients ≤18 yr	2 (10)	3 (13)	1 (6)
KPS <sup>a</sup>			
Median	90	80	80
Minimum	50	50	50
Maximum	100	100	100
Tumor classification			
Primitive neuroectodermal tumor	7 (37)	4 (17)	1 (6)
Astrocytoma	2 (10)	4 (17)	3 (18)
Glioblastoma	3 (16)	2 (8)	3 (18)
Metastatic cancer to the brain	4 (21)	1 (4)	3 (18)
Relapsed CNS lymphoma	1 (5)	2 (8)	3 (18)
Oligoastrocytoma	0 (0)	4 (17)	0 (0)
Oligodendroglioma	0 (0)	2 (8)	1 (6)
Anaplastic oligodendroglioma	0 (0)	1 (4)	2 (12)
Brain stem glioma	1 (5)	2 (8)	0 (0)
Optic glioma	0 (0)	2 (8)	0 (0)
Retinoblastoma	0 (0)	0 (0)	1 (6)
Germ cell	1 (5)	0 (0)	0 (0)

<sup>a</sup> KPS: Karnofsky Performance Status.

Table 2 Number of patients in each group at each treatment

Treatment no.	HCG (n = 19)	STS2 (n = 24)	STS4 (n = 17)
1	19	24	17
2	19	19	15
3	17	17	11
4	17	15	8
5	14	14	8
6	11	11	7
≥7	9	9	6

carboplatin treatment. Four patients in STS4 were in the midst of the year-long carboplatin treatment at the time of the cutoff for data analysis.

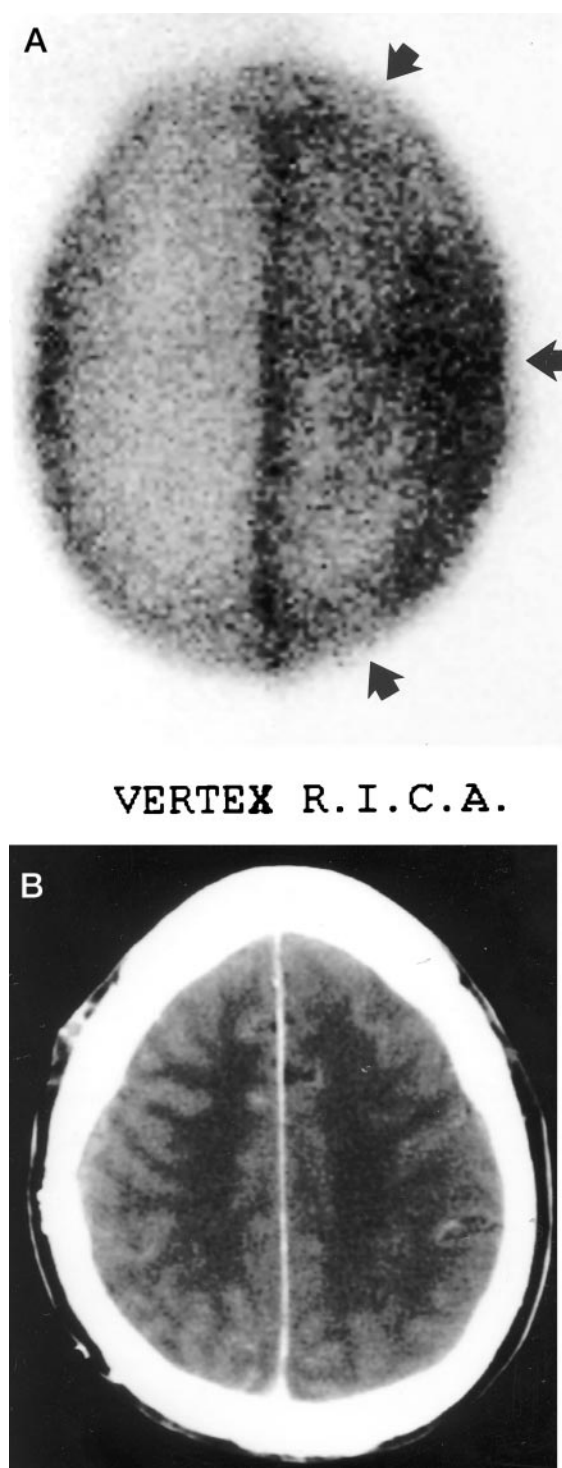
**Two-compartment Model.** Fig. 2, A and B, illustrate the two-compartment model created by transiently opening the BBB. Fig. 2A shows a <sup>99m</sup>Tc-glucoheptonate radionuclide brain scan with isotope given 5 min after the delivery of hypertonic mannitol into the RICA, illustrating the BBB opening in the right cerebral hemisphere. A computed tomography scan obtained in the same patient with iodinated contrast given 60 min after mannitol (Fig. 2B) shows minimal contrast enhancement in the disrupted hemisphere, illustrative of a barrier that has almost completely returned to baseline permeability by 1 hour. Carboplatin was administered i.a. immediately after osmotic opening of the BBB, thus crossing the opened BBB. STS

was then administered i.v. 2 or 4 h after BBBD, after BBB permeability generally returned to baseline levels. Pollay *et al.* (45) reported previously that the highly charged STS molecule does not cross the BBB.

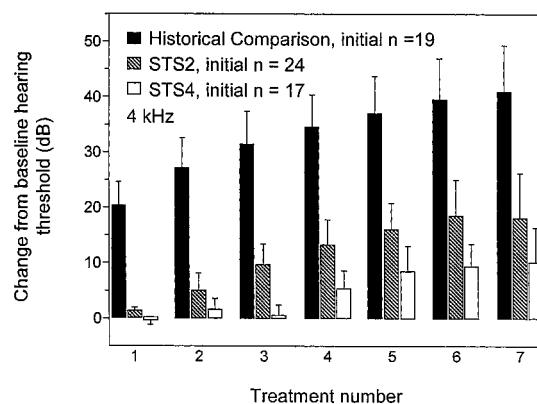
**Efficacy of STS in Maintaining Hearing Sensitivity.**

The full repeated-measures ANCOVA model had several significant three-way interactions involving test frequency. For this reason, frequency-specific models were fit to better understand any group differences. At 8000 Hz and at 4000 Hz, after adjusting for baseline hearing levels, there were significant differences among the treatment groups ( $P = 0.0010$  and  $P = 0.0075$ , respectively) and significant linear ( $P = 0.0002$  and  $P = 0.0001$ , respectively) and quadratic trends (at 4000 Hz only;  $P = 0.035$ ) with treatment. The least-squares means (see “Materials and Methods”) for treatment groups (in order: 4-h protocol, 2-h protocol, and historical comparison) were 34.1 dB, 41.7 dB, and 64.4 dB at 8000 Hz and 28.6 dB, 35.4 dB, and 51.6 dB at 4000 Hz. There were significant differences between each of the STS groups and the historical comparisons, but no significant differences between the two STS groups. For the 1000 and 2000 Hz frequencies, there were no significant differences among the treatment groups once the Bonferroni adjustment was used. For 500 and 250 Hz, after adjustment for baseline hearing levels, there were no significant treatment effects.

Fig. 3 compares the average change in thresholds from baseline against carboplatin treatment number, at 4000 Hz, in



**Fig. 2** A patient underwent osmotic opening of the BBB with infusion of hypertonic mannitol into the RICA. A, 99 m Tc-glucoheptonate was given i.v. 5 min after the hypertonic mannitol. Radionuclide brain scan was done 3 h after radionuclide was given. Vertex view documents BBB opening in the right cerebral hemisphere (arrows). B, Oxilan, 150 ml was given i.v. 55 min after the radionuclide (60 min after hypertonic mannitol). Computed tomography head scan was done immediately after contrast (Oxilan) administration. There is a lack of enhancement in the right cerebral hemisphere at 1 h, illustrating BBB closure in that region, in contrast to A, which shows BBB opening at 5 min.



**Fig. 3** Comparison of threshold shift against carboplatin treatment number, at 4000 Hz, in the historical comparison patients who received carboplatin without STS and in patients treated with delayed STS 2 h (STS2) or 4 h (STS4) after carboplatin. There was a significant difference between the STS treatment groups and the HCG ( $P = 0.0075$ ).

HCG, STS2, and STS4. There was a significant difference between the STS treatment groups and the HCG ( $P = 0.0075$ ).

**Delay in Onset of Ototoxicity.** The Kaplan-Meier estimates of the time to ototoxicity are plotted against treatment in Fig. 4. There is a significant difference among the three treatment groups using the log-rank test ( $P = 0.0069$ ). The difference between the 4-h protocol and the historical comparisons is statistically significant ( $P = 0.0018$ ), whereas the differences between the 2-h protocol and the historical comparisons ( $P = 0.0730$ ) and the 2-hour protocol and the 4-hour protocol ( $P = 0.12$ ) are not significant. These  $P$ s need to be compared with a significance level of 0.0167, as described in "Materials and Methods."

Over the study period, 84% of the historical comparisons experienced ototoxicity, whereas only 54% of the patients on the 2-h protocol and 29% of the patients on the 4-hour protocol experienced ototoxicity. The Spearman correlation coefficient comparing the ordered treatment groups with ototoxicity or not yielded a correlation of  $-0.43$  ( $P = 0.0006$ ). These analyses illustrate significantly lower rates of ototoxicity as one progresses from no STS to an STS 2-h protocol to an STS 4-h protocol.

## DISCUSSION

**Potential for Delayed STS in CNS and Non-CNS Tumors.** Otoprotection in patients undergoing carboplatin treatment in conjunction with osmotic opening of the BBB can be achieved with high-dose STS administered 2 or 4 h after carboplatin. The greater the delay in STS administration (from HCG to STS2 to STS4), the lower the rate of ototoxicity ( $P = 0.0006$ ). There is a significant difference between STS administered at 4 h and the HCG, with respect to time to ototoxicity and maintenance of hearing sensitivity at 8000 Hz ( $P = 0.0010$ ) and 4000 Hz ( $P = 0.0075$ ) and a trend toward differences between STS administered at 2 h and at 4 h in delaying ototoxicity and in maintaining hearing sensitivity, however the sample size is not large enough to demonstrate statistical significance.

The efficacy of delayed STS administration is important.

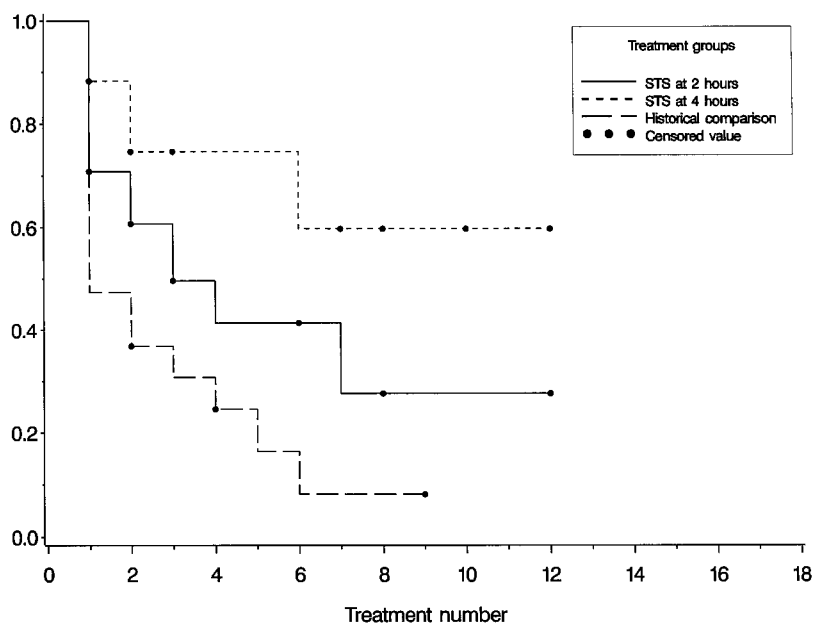


Fig. 4 Effect of STS on time to development of ototoxicity. Kaplan-Meier graph plots proportion of patients with no ototoxicity. HCG and patients treated with delayed STS at 2 (STS2) or 4 h (STS4) after carboplatin are plotted separately. The STS4 group is statistically different from the HCG ( $P = 0.0018$ ). A censored value indicates the patient had no ototoxicity at their last audiological assessment.

Muldoon *et al.* (38) reported that, in an animal model, delayed administration of STS up to 8 h after carboplatin reduced ototoxicity without reducing the antitumor cytotoxicity of carboplatin. If STS prevents ototoxicity in patients at even later time points (*e.g.*, 8 h) than in this clinical study, treatment with STS may be applicable both to other platinum agents such as cisplatin and to non-CNS tumors. Eight-hour delayed administration of STS would ensure adequate time for non-CNS platinum cytotoxicity to occur. To test such a hypothesis, our group has developed a clinical protocol for children undergoing cisplatin treatment for osteosarcoma, germ cell tumor, PNET, and neuroblastoma. In addition, although carboplatin does not have equivalent activity to cisplatin in all platinum-sensitive tumors, carboplatin use is increasing in some cancers [suboptimally debulked ovarian cancer and non-small cell and extensive-stage small cell lung cancer (4)] because of similar efficacy and fewer toxic attributes, and higher doses of carboplatin are being used to increase antitumor efficacy (28, 46). As carboplatin doses are intensified, the incidence of ototoxicity must be closely monitored.

**Mechanism of the Carboplatin-STS Chemoprotective Reaction.** Although the mechanism of STS otoprotection at the molecular level is unknown, we hypothesize that there is direct interaction with hair cells of the cochlea to rescue them from carboplatin that is already bound to cellular targets (38). *In vitro*, STS binds directly to the electrophilic platinum, rendering the platinum inactive. A delay between the administration of carboplatin and the administration of STS allows the rapid clearance of these drugs to reduce the concentration of free carboplatin available to interact with STS. A delay in administration provides for a high molar ratio of STS to carboplatin; thus there is more STS to deactivate the remaining free carboplatin as well as carboplatin bound to cellular targets (38). In animal studies, when STS was administered 8 h after carbopla-

tin, a time point at which STS remained otoprotective, serum platinum concentrations were near zero.

**Effect of STS on Carboplatin Cytotoxicity.** Despite a two-compartment model and the high ratio of STS:carboplatin required to inactivate carboplatin (27, 35–37), the possibility remains that STS reduces carboplatin tumoricidal effect. Because of the varying CNS tumor histologies and the small number of patients within each histological category in HCG, STS2, and STS4 (Table 1), it is not yet possible to determine whether or not there is an effect of STS on clinical outcomes such as tumor response. We continue to closely monitor response rates. For example, patients in STS2 and STS4 with PNET ( $n = 5$ ), astrocytoma ( $n = 7$ ), and glioblastoma ( $n = 5$ ) had the following tumor responses: (a) PNET: one complete response, three partial responses, and one SD; (b) astrocytoma: three partial responses and four SDs; (c) glioblastoma: four SDs, 1 progressive disease. In the future, with a larger series of patients with more homogenous CNS malignancies and with continued monitoring of tumor responses, a more definitive analysis of the effect of STS on clinical outcomes will be possible.

**Quality of Life.** Loss of pure-tone sensitivity in the 2000–4000 Hz frequency range results in difficulty discriminating consonant sounds. This difficulty is exacerbated when attempting to identify words in the presence of background noise (28). Hearing loss exceeding 20 dB HL in the speech frequencies thus impacts family and social interaction as well as work status. Children with hearing impairment are at risk for problems with learning and communication (30). In the pediatric population, with loss of sensitivity in the 2000–4000 Hz range, a hearing aid is often required to optimize learning skills. In the hearing-impaired elderly population, studies have documented impairment in functional status, cognitive status, depressive symptomatology, and disability (31, 32).

Maximizing quality of life is essential in patients with limited survival. Strategies to achieve dose intensification and maximum cytotoxicity necessitate interventions to minimize the associated toxicities and to protect against untoward side effects of effective chemotherapeutics. Given the impact of hearing loss on quality of life in patients undergoing platinum chemotherapy, identification of agents to decrease ototoxicity is essential. We propose that clinical trials to evaluate 8-h delayed administration of STS in children, and subsequently in adults, undergoing cisplatin chemotherapy for non-CNS as well as CNS tumors may extend these positive results.

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