Use of Sodium Thiosulfate as an Otoprotectant in Patients With Cancer Treated With Platinum Compounds: A Review of the Literature

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ABSTRACT

PURPOSE Hearing loss occurs in 50%-70% of children treated with cisplatin. Scientific efforts have led to the recent approval of a pediatric formula of intravenous sodium thiosulfate (STS) for otoprotection by the US Food and Drug Administration, the European Medicines Agency, and the Medicines and Health Regulatory Authority in the United Kingdom. To inform stakeholders regarding the clinical utility of STS, the current review summarizes available literature on the efficacy, pharmacokinetics (PK), and safety of systemic STS to minimize cisplatin-induced hearing loss (CIHL).

DESIGN A comprehensive narrative review is presented.

RESULTS Thirty-one articles were summarized. Overall, systemic STS effectively reduces CIHL in the preclinical and controlled clinical study settings, in both adults and children with cancer. The extent of CIHL reduction depends on the timing and dosing of STS in relation to cisplatin. Both preclinical and clinical data suggest that systemic STS may affect plasma platinum levels, but studies are inconclusive. Delayed systemic administration of STS, at 6 hours after the cisplatin infusion, does not affect cisplatin-induced inhibition of tumor growth or cellular cytotoxicity in the preclinical setting, nor affect cisplatin efficacy and survival in children with localized disease in the clinical setting.

CONCLUSION Systemic administration of STS effectively reduces the development and degree of CIHL in both the preclinical and clinical settings. More studies are needed on the PK of STS and cisplatin drug combinations, the efficacy and safety of STS in patients with disseminated disease, and the ability of STS to prevent further deterioration of pre-established hearing loss.

ACCOMPANYING CONTENT

Appendix

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INTRODUCTION

Platinum compounds have contributed significantly to increased survival rates in children with solid tumors including osteosarcoma, germ cell tumors, hepatic tumors, neuroblastoma, nasopharyngeal carcinoma, retinoblastoma, and medulloblastoma. However, ototoxicity in the form of irreversible hearing loss, tinnitus, and vestibular dysfunction is a consequence of this chemotherapy. Estimates suggest that some degree of cisplatin-induced hearing loss (CIHL) develops in 50%-70% of treated children.[1-6] The main mechanism whereby cisplatin damages the inner ear is the formation of high levels of reactive oxygen species (ROS), eventually resulting in cochlear hair cell apoptosis.[7,8] Hearing loss related to carboplatin treatment is also observed, but the overall prevalence is lower (0%-25%).[9-14] Ototoxic effects are thought to be more pronounced in patients who receive both cisplatin and carboplatin, with prevalence rates of 75% reported.[13,15] In young children (age 5 years and younger), the cumulative incidence of CIHL is higher compared with that in older children (older than 5 years) and develops early during therapy.[16]

Other treatment-related risk factors may induce or enhance ototoxic effects, including vincristine administration,[17] cranial irradiation,[18] brain surgery,[19] and supportive care medication.[16] Genetic susceptibility may explain why certain patients are more prone to developing CIHL compared with others who receive similar treatments.[20]

CIHL can negatively affect daily functioning by delayed speech and language development,[21] reduced academic

performance,[22] impaired neurocognitive functioning,[23] social isolation, emotional deprivation, and consequent impaired quality of life (QoL)[24] compared with peers without hearing loss. In later life, hearing loss may affect cognition[25] and has been sighted as a risk factor for dementia.[26-28] This may occur directly, through changes in auditory input affecting the brain structures responsible for cognition, or indirectly through factors such as heightened social isolation, depression, impaired self-confidence, reduced physical activity, or decreased engagement in intellectually stimulating activities.[29-31] This is particularly concerning as pediatric patients with cancer are already at risk for comorbidities, including accelerated aging[32] and impaired QoL.[33,34]

Given the high prevalence and clinical impact of CIHL, it would be advantageous to reduce or, preferably, prevent this permanent toxicity as much as possible. Reducing the dose of cisplatin, or replacing it with another chemotherapeutic agent, requires randomized clinical trials to prove equal efficacy, otherwise this could negatively affect survival.[35] The advent of preventative agents to reduce CIHL is clearly welcome.

The otoprotective effect of sodium thiosulfate (STS) has been explored across multiple studies over several decades, either via systemic or local administration. STS is thought to reduce cisplatin-induced toxicity by two mechanisms. First, STS can bind to cisplatin, leading to the formation of inactive cisplatin compounds. Second, STS enters cochlear cells via cotransporter-2, where it influences antioxidant enzymes. It elevates antioxidant glutathione levels inhibiting intracellular ROS formation induced by cisplatin.[36,37] Systemic administration requires a sufficient amount of STS to cross the blood-labyrinth barrier to obtain a preventative effect. Local applications such as intratympanic and intracochlear injections, administering STS directly to the ear, are not the subject of this review.[38,39]

Scientific evidence, alongside results from two randomized pediatric clinical trials,[40,41] have recently led to marketing authorization for intravenously (IV) administered pediatric STS, by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the UK Medicines and Health Regulatory Authority (MHRA). Currently, this compound is licensed as a cisplatin otoprotectant, for children age 1 month or older, who have nonmetastatic solid tumors (neuroblastoma, hepatoblastoma, nasopharyngeal carcinoma, osteosarcoma, germ cell tumors, medulloblastoma, and other rare tumors), at a dose of 10-20 g/m^2 (dependent on body weight) administered over 15 minutes, 6 hours after the end of the cisplatin infusion.[42]

A recent survey showed that North American health care providers consider CIHL to be a concerning toxicity.[43] It is therefore important that all stakeholders are well informed on the use of STS. To date, an overview of all studies on STS is lacking. This review summarizes available literature (N = 31) on the efficacy, pharmacokinetics (PK), and safety of systemic STS in the prevention of CIHL. The majority of this article pertains to cisplatin, although mention will be made of STS and carboplatin.

OTOPROTECTIVE EFFECT OF SYSTEMIC STS

Preclinical Studies

In 1988, Otto et al[44] first described the otoprotective effect of STS in vivo. They injected 17 guinea pigs with intramuscular (IM) cisplatin for 8 days (1.5 mg/kg total per day), and 11 with cisplatin and STS (16 g/kg total per day). At 10 days after cisplatin, auditory brainstem responses (3-30 kHz) were measured and converted to hearing threshold levels (HTLs). In cisplatin only-treated animals, a HTL shift of >40 dB from baseline was observed at all frequencies, whereas the HTLs in the STS group remained unchanged.[44] Four other studies performed between 1995 and 2000 completed similar experiments in hamsters and guinea pigs, which also reported normal HTLs (0-20 dB) at ≥30 days after cisplatin and after carboplatin in animals that received STS.[45-48] One other study (N = 14) only found a significant difference in favor of STS in the very high frequency range (30 kHz; $P = .07$).[49]

Dickey et al[50] specifically assessed HTLs when IV STS (8 g/m^2) was administered at different time points after a single infusion of intra-arterial (IA) cisplatin (6 mg/kg). Compared with rats treated with cisplatin only (N = 15), a significant difference in favor of STS was found when it was administered at 4 or 8 hours after cisplatin (n = 7: $P < .05$), but not after 12 hours.[50]

Cochlear outer hair cells (OHCs) have also been assessed in multiple studies. Cisplatin-treated rodents showed a reduction in number of OHCs of 32%-65%, whereas only minor losses of 5%-14% were reported in animals receiving STS.[45-47] Overall, the studies show that systemic STS effectively reduces the development of hearing loss, and this may vary with the timing of administration (Table 1).

Clinical Studies

Historically, STS was administered systemically at the same time as cisplatin, the goal being to increase the dose of cisplatin without increasing toxicity.[51-60] This approach changed in more recent clinical studies, where different approaches to the administration of STS were investigated to avoid interference with the antitumor effect of IV cisplatin on the one hand and IA carboplatin on the other: (1) separating IV STS from IV cisplatin by time (eg, 6 hours after the end of cisplatin infusion) with the aim of avoiding STS being in the circulation alongside peak serum cisplatin levels (to avoid interference with the antitumor effect of cisplatin while retaining an otoprotective effect)[40,41]; and (2) separating IV STS from IA carboplatin by space, specifically via blood-brain barrier disruption (BBBD; Appendix Fig A1, online only). To increase the IA

TABLE 1. Preclinical Studies on the Otoprotective Effect of STS

Author, Year	Species	No.: STS Group	No.: Comparison Group	Platinum Treatment	STS Specification	Evaluation Methods	FU Time, Post-Tx	Hearing Function Outcomes		*P*	OHC Count
								With STS	Without STS		
Otto et al,[44] 1988	Guinea pig	11: CIS + STS	17: CIS only 10: normal saline	CIS IM 1.5 mg/kg total per day 8 days	STS IP 16 g/kg total per day Concurrent with CIS	ABR (3-30 kHz)	10 days	No HTL shift from baseline	>40 dB HTL shift from baseline	NA	—
Church et al,[45] 1995	Hamster	10: CIS + STS	10: CIS only 22: no Tx	CIS IP 3 mg/kg total per day EOD 5 injections	STS IP 16 g/kg total per day Concurrent with CIS	ABR (2-20 kHz) Electron microscopy	30 days	HTLs <10 dB at all frequencies	HTLs 30-48 dB at 8-20 kHz	NA	Untreated: N = 2,672 CIS only: 32% loss CIS + STS: 14% loss
Neuwelt et al,[46] 1996	Guinea pig	6: CARBO + STS	12: CARBO only 6: saline	CARBO SC 24 mg/kg 1 injection	STS IP 1.83 g/kg 2, 4, 8, and 24h after CARBO	CAP (2-32 kHz) OHC count (unspecified)	4 weeks	HTLs 0-10 dB at all frequencies	HTLs 40-60 dB at all frequencies	NA	CARBO only: 65% loss CARBO + STS: 5% loss
Kaltenbach et al,[47] 1997	Hamster	10: CIS + STS	10: CIS only 4: no Tx	CIS IP 3 mg/kg 5 injections	STS IP 16 g/kg 30 min before CIS	ABR (2-20 kHz) Electron microscopy	30-35 days	HTLs 10 dB at all frequencies	HTLs 50 dB at 16 kHz	NA	Untreated: N = 2,670 CIS only: 44% loss CIS + STS: 9% loss
Muldoon et al,[48] 2000	Guinea pig	2: CIS + STS	2: CIS + saline	CIS IV 6 mg/kg 1 infusion	STS bolus IP or 15-min IV infusion 11.6 g/m^2 2h after CIS	ABR (4-32 kHz)	8 weeks	HTLs 0-20 dB at all frequencies	HTLs 30-50 dB at all frequencies	NA	—
Dickey et al,[50] 2005	Rat	7: CIS + STS	15: CIS + saline	CIS IA 3 mL/min 6 mg/kg 1 infusion	STS IV 8 g/m^2 4, 8, and 12h after CIS	ABR (4-20 kHz)	7 days	STS 4h: HTLs 0-5 dB at all frequencies STS 8h: HTLs 0-10 dB at all frequencies STS 12h: HTLs 10-20 dB at all frequencies	HTLs 10-25 dB at all frequencies HTLs 10-20 dB at all frequencies HTLs 10-30 dB at all frequencies	<.05 <.05 >.05	—
Videhult Pierre et al,[49] 2017	Guinea pig	7: CIS + STS	7: CIS + saline	CIS IV in 3 min 8 mg/kg 1 infusion	STS 20 sec IV infusion 1 mL/0.3 kg 30 min before CIS	ABR (3-30 kHz)	4 days	HTLs 0-25 dB at all frequencies	HTLs 5-35 dB at all frequencies	.07 (only at 30 kHz)	—

Abbreviations: ABR, auditory brainstem response; CAP, compound action potential; CARBO, carboplatin; CIS, cisplatin; EOD, every other day; FU, follow-up; HTL, hearing threshold level; IA, intra-arterial; IM, intramuscular; IP intraperitoneal; IV, intravenous; NA, not assessed; OHC, outer hair cell; SC, subcutaneous; STS, sodium thiosulfate; Tx, treatment.

delivery of carboplatin across the BBB, transient osmotic disruption of the barrier via mannitol is used. After 2 hours, the BBB is re-established and IV STS is administered (Appendix Fig A1).[61-63] BBBD studies evaluate STS in patients with CNS tumors treated with IA carboplatin. In these studies, STS is used to counteract carboplatin in the circulation and potentially mitigate the effects of carboplatin on organs outside of the CNS.

STS Studies With a Control Group

Randomized Controlled Trials

Brock et al[40] designed the SIOPEL 6 trial in which 109 children with standard-risk hepatoblastoma were randomly assigned to receive treatment with six cycles of single-agent IV cisplatin (80 mg/m²) and surgery with (n = 57) or without (n = 52) IV STS (20 g/m²), administered 6 hours after the end of the cisplatin, as a 15-minute infusion. Patients in each arm were matched by tumor type, prognostic group, and treatment received. Pure tone audiometry (PTA) showed that the incidence of hearing loss in those who received cisplatin only was 63%, compared with 33% in the STS group (P = .002; relative risk, 0.52 [95% CI, 0.33 to 0.81]) and that the grade of hearing loss was significantly less in those who received STS.[40] A similar observation was reported by Freyer et al[41] in the ACCL0431 STS otoprotection trial. Children with any type of tumor treated with cisplatin (290-466 mg/m²) were eligible and randomly assigned to receive IV STS 16 g/m² over 15 minutes, 6 hours after the end of the cisplatin infusion (n = 49) or not (n = 55). Patients were not matched by tumor type, biology, stage, risk, or treatment. A significant reduction of hearing loss in the STS group (29%) compared with the observation group (56%; P = .00022)[41] was observed.

Non-RCTs

In adults who received IA carboplatin after BBBD for CNS tumors (N = 15), Doolittle et al[61] showed that the percentage of hearing loss (at 4 and 8 kHz) was 52%, compared with historical controls who received no STS, when IV STS (16-20 g/m²) was administered 2 hours after carboplatin, and improved to only 29% when STS was given after 4 hours. In an earlier phase II study, Neuwelt et al[62] reported 33% hearing loss in 15 patients who received IV STS at 16 or 20 g/m² after IA carboplatin following BBBD, compared with a small number of patients who received STS at a dose of four or 8 g/m² (n = 4). These BBBD studies show that delayed timing of STS in relation to carboplatin administration as well as a higher dose of STS both increase the extent of the hearing protection.

Adults with head and neck squamous cell carcinoma (HNSCC) who received cisplatin (IV or IA, 66-100 mg/m²) with STS (12-14 g/m² over 2-4 hours) at the same time revealed minor yet significant mean differences in HTL shifts up to 4 kHz (5.3 dB in the STS group *v* 8.9 dB in the non-STS group; P < .001)[60] and at higher frequencies (20 dB at 10-12 kHz *v* 15-25 dB at 8-10 kHz, respectively: lowest P = .016).[53]

The most common mild-to-moderate adverse events related to systemic STS reported include nausea and vomiting, nephrotoxicity, neutropenia, hypernatremia, hypophosphatemia, hypokalemia, and hypermagnesemia,[40,41,62] and no late side effects have been reported to date.

In summary, systemic STS has been shown to effectively reduce the occurrence of hearing loss in controlled clinical studies in both adults and children with cancer. In children, RCTs have only been pursued with one specific STS compound. Otoprotection seems to depend on the dosing of STS and timing of administration (Table 2).

STS Studies Without a Control Group

Since 1982, several clinical studies (mainly phase I or II trials) have investigated the concomitant administration of STS with cisplatin, either to increase the dose of cisplatin to enhance treatment efficacy, or to reduce platinum-related toxicities (including hearing loss).[51,52,54-59,63-66] Reichman et al[57] performed PTA (up to 20 kHz) in 11 adults with cervical cancer, who received IV cisplatin over 2 hours (200 mg/m²; 2-5 courses) with IV STS (3.3-6.6 g/m²) at the same time. After the first course, 44% developed hearing loss at >8 kHz. Thereafter, 77% developed hearing loss at 8 kHz; 55% at 6 kHz; and 11% at 1-4 kHz.[57] Kim et al[54] (1993) reported 50% hearing loss during treatment in 18 adults with different tumor types, who received IV cisplatin over 6 hours (180 mg/m² for 1-6 cycles) with STS (2-4 g/m²). One study observed 10% self-reported moderate-to-severe hearing loss, in adults with HNSCC (N = 79), treated with IA cisplatin (150 mg/m² for four courses) administered at the same time as IV STS (12 g/m² for 2 hours).[51] Two comparable studies in populations with the same diagnosis and treatment reported 60% CIHL after end of treatment as measured by PTA (N = 70),[65] and 23% of evaluated ears to be under consideration for hearing aids at 7.5 weeks after the last cisplatin cycle (N = 146).[59]

Continuous hearing deterioration was reported after cisplatin + STS in adults with pre-existing hearing loss (ie, present before start of cancer treatment),[55,58] and in a child with CIHL who received STS near the end of the cisplatin regimen with the goal to avoid a further decrease of HTLs.[64] Neuwelt et al[63] found differences in hearing loss occurrence between children who received IV STS at 2 hours versus 4 hours after BBBD + IA carboplatin, with percentages of 60% and 33% (loss of ≥40 dB at 2-8 kHz) reported, respectively. An additional study performed in adolescents and young adults (N = 13)[66] reported a hearing loss incidence of 46% after intraperitoneal (IP) treatment with hyperthermic cisplatin (55-100 mg/m²) in parallel with IV STS administered over 12 hours. As the studies described above did not include control groups, a conclusion on the otoprotective

TABLE 2. Clinical Studies on the Otoprotective Effect of STS (with a control group)

Author, Year	Design	Patient Characteristics	No.: STS Group	No.: Comparison Group	Platinum Treatment	STS Specification	Audiometry	FU Time	Hearing Function Outcomes		*P*	Adverse Events	Survival
									With STS	Without STS			
Studies in adults													
Zuur et al,[60] 2007	RCT: phase 3	HNSCC Median age: 55 years	78: CIS + STS + radiotherapy (70 Gy)	80: CIS only + radiotherapy (70 Gy)	CIS + STS CIS IA; 4× 150 mg/m^2 CIS only CIS IV; 3× 100 mg/m^2	STS IV 9 g/m^2 for 30 minutes + 12 g/m^2 for 2 hours Concurrent with CIS	PTA 0.25-16 kHz	Median: 8 weeks post-Tx	HTL shifts >10 dB over time Mean HTL shift up to 4 kHz: 5.3 dB, and up to 12.5 kHz: 20.4 dB	HTL shifts >10 dB over time Mean HTL shift up to 4 kHz: 8.9 dB, and up to 12.5 kHz: 19.0 dB	<.001 (≤4 kHz)	NA	NA
Ishikawa et al,[53] 2015	Prospective cohort study	HNSCC Age: 45-82 years	7: CIS + STS + radiotherapy (60-70 Gy)	11: CIS only + radiotherapy (60-70 Gy)	CIS + STS CIS IA; 2-5× 100-180 mg/m^2 CIS only CIS IV; 1-3× 66-85 mg/m^2	STS IV 14 g/m^2 for 4 hours Concurrent with CIS	PTA 0.125-12 kHz	1-3 weeks post-Tx	From baseline HTL shifts of 20 dB at 10 and 12 kHz	From baseline HTL shifts of 15-25 dB at 8 and 10 kHz	.028 .039 .016 .027	NA	NA
Studies in mixed cohorts of children and adults													
Neuwelt et al,[62] 1998	Cohort study STS group: prospective Comparison group: retrospective	Brain tumors Age: 2-68 years	15: CARBO + STS 16 or 20 mg/m^2 4: CARBO + STS 4 or 8 mg/m^2	19: CARBO only	BBBD + CARBO IA over 10-min 400 mg/m^2 per month 4-12 courses	STS IV over 15 minutes 4-20 mg/m^2 2 hours after CARBO	PTA 0.25-8 kHz	Each month during Tx	HL in 33% with STS 16 or 20 mg/m^2[a] Average loss after first cycle: 3.7 ± 2.0 dB at 8 kHz	HL in 79% Average loss after first cycle: 20.8 ± 5.9 dB at 8 kHz	<.05	Mild nausea, vomiting HN, ↑ blood pressure	NA
Doolittle et al,[61] 2001	Cohort study STS group: prospective Comparison group: retrospective	Brain tumors Age: 4-67 years	24: CARBO + STS after 2 hours 17: CARBO + STS after 4 hours	19: CARBO only	BBBD + CARBO IA over 10-min 400 mg/m^2 per month 1-7 courses	STS IV over 15 minutes 16 or 20 mg/m^2 2 or 4 hours after CARBO	PTA 0.25-8 kHz	Each month during Tx	STS2h: HL in 52% HTL shift at 8 and 4 kHz: 41.7 dB and 35.4 dB, respectively STS4h: HL in 29% HTL shift at 8 and 4 kHz: 34.1 dB and 28.6 dB, resp.	HL in 84% HTL shift at 8 and 4 kHz: 64.4 dB and 51.6 dB, respectively	.001 (at 8 kHz) .0075 (at 4 kHz)	NA	NA
Studies in children and adolescents													
Freyer et al,[41] 2017	RCT: multicenter, open-label, phase 3	Any tumor Age: 1-18 years	49: CIS + STS	55: CIS only	CIS IV 6× CIS + STS: 393 mg/m^2 (290-420) CIS only: 387 mg/m^2 (305-466)	STS IV over 15 minutes 16 g/m^2 6 hours after CIS	PTA 0.5-8 kHz	4 weeks post-Tx EFS + OS: median 3.5 years	HL in 29%	HL in 56%	.00022	Nephrotoxicity HP, HK	EFS + OS in both groups: *P* = .36 and .07, respectively EFS + OS in LD (N = 77): *P* = .73 and .88, respectively OS in DD (N = 47): *P* = .009
Brock et al,[40] 2018	RCT	SR HBL Age: 0-8 years	57: CIS + STS	52: CIS only	CIS IV 6× 80 mg/m^2	STS IV over 15 minutes 20 mg/m^2 6 hours after CIS	PTA 1-8 kHz	During Tx EFS + OS: median 3.0 years	HL in 33%	HL in 63%	.002	Neutropenia, HM, HP, HK	3-yr EFS in CIS + STS group: 82%, 95% CI 69%-90%; in CIS alone group 79%, 95% CI 65%-88% 3-yr OS CIS + STS: 98%, 95% CI 88%-100%; CIS alone 92%, 95% CI 81%-97%

Abbreviations: BBBD, blood-brain barrier disruption; CARBO, carboplatin; CIS, cisplatin; DD, disseminated disease; EFS, event-free survival; FU, follow-up; HBL, hepatoblastoma; HK, hypokalemia; HL, hearing loss; HM, hypermagnesemia; HN, hypernatremia; HNSCC, head and neck squamous cell carcinoma; HP, hypophosphatemia; HTL, hearing threshold level; IA, intra-arterial; IV, intravenous; LD, localized disease; NA, not assessed; OS, overall survival; RCT, randomized controlled trial; SR, standard risk; STS, sodium thiosulfate; Tx, treatment.

[a]Most patients who received 4 or 8 mg/m^2 developed hearing loss.

effect of STS in these populations is hard to ascertain, although the comparison between 2-hour versus 4-hour delay in administration of STS confirms the advantage of the longer delay (Table 3).

PK OF PLATINUM AND SYSTEMIC STS

Preclinical Studies

Saito et al[67] investigated the effect of systemic STS on the PK of cisplatin. Guinea pigs received three injections of IM cisplatin (7.5 mg/kg) with (n = 24) or without (n = 15) IP STS (1,000 mg/kg), administered concurrently with cisplatin, and 1-6 hours thereafter. Free cisplatin (FP) and total cisplatin (TP) were analyzed by inductively coupled mass spectrometry (ICP-MS). In terms of elimination, lower FP and TP concentrations were found in plasma of guinea pigs who received STS at 6 and 24 hours ($P < .05$).[67] By contrast, Harned et al[68] did not observe differences in cisplatin concentrations in plasma at 6 hours after administration in eight mice treated with IP cisplatin (4 mg/kg total per day for 4 days) and IP STS (3.5 g/kg total per day) compared with two mice that received cisplatin only, as measured by atomic absorption spectrometry (AAS).

To date, to our knowledge, only one study has investigated the effect of systemic STS on the PK of carboplatin by using AAS. In guinea pigs, C_{max} in plasma (ie, the peak plasma concentration) was approximately 23 μg/mL in both groups that received carboplatin (24 mg/kg) with STS (11.6 g/m² administered 2 hours after carboplatin), and carboplatin area under the plasma concentration-time curve (AUC) values were also comparable (61 μg/mL/h in the group with STS and 69 μg/mL/h in those without STS). Carboplatin clearance was reported to be similar in groups treated with and without STS (208 and 184 mL/h/kg, respectively: $P = .33$).[48]

In 10 guinea pigs that received IV STS (103 mg/kg) without cisplatin or carboplatin, the maximum concentration of STS was observed 10 minutes after administration (C_{max} mean: 300 μM), with very low STS concentrations observed at 200 minutes after administration (mean: 1.5 μM), assessed in plasma by high-performance liquid chromatography (HPLC) analysis.[69] Because of faster elimination from the bloodstream, the concentration of STS measured in the perilymph of the inner ear exceeded that of blood at the later time point, with mean perilymph concentrations of 55 μM and 7.0 μM observed at 10 and 200 minutes, respectively.

Because of different study end points and reported PK outcomes, a conclusion on the effect of systemic STS on cisplatin and carboplatin levels cannot be drawn (Table 4).

Clinical Studies

Howell et al[52] studied the effect of STS on the PK of cisplatin in 17 adults with IP tumors, who received IP cisplatin administered by dialysis over 4 hours (90-270 mg/m²) with IV STS over 12 hours (2.13 g/m²). Blood was obtained every 60 minutes after cisplatin and analyzed using HPLC. Cisplatin C_{max} in plasma was 7.5 μg/mL and no effect of STS administration was observed ($P > .05$). This was also the case for $t_{1/2}$ (half-life), which remained around 50-60 minutes in plasma when STS was added ($P > .05$).[52] Similar observations have been reported by Pfeifle et al.[56] In adults with different tumor types who received IV cisplatin (100 mg/m²) without STS (n = 5) or IV cisplatin (200 mg/m²) with IV STS (3.3-9.9 g/m²; n = 6) for 3 hours, no significant differences were observed in $t_{1/2}$ (36.5 *v* 38.5 minutes, respectively) or plasma clearance (222 *v* 234 mL/min/m², respectively). Similarly, plasma C_{max} and AUC were approximately twice as high for the group of patients receiving the higher dose of cisplatin, suggesting that STS did not affect cisplatin PK.[56] In a study by Goel et al[70] in 14 adults treated concurrently with IP cisplatin (90 mg/m²) and STS (12 g/m² over 6 hours), a nonsignificant reduction in the mean total plasma AUC from 8.8 μg/mL/h without STS to 6.7 μg/mL/h with STS was reported up to 21 hours (25%; $P > .05$). This difference became significant for the last 3 hours of exposure (up to 24 hours) with a reduction of 54% ($P < .05$).[70]

On the basis of the studies described above, it seems unlikely that STS has a major impact on systemic cisplatin PK levels even when the drugs are administered concurrently, but a firm conclusion on this is not possible to draw and requires further research. This is currently being assessed in the ongoing Paediatric Hepatic International Tumour Trial (PHITT; ClinicalTrials.gov identifier: NCT03017362). In all studies, platinum was measured (not specifically cisplatin or carboplatin), consisting of intact drug, aqua complexes, and platinum-bound species (including STS-bound platinum) being measured simultaneously. It is therefore unknown whether systemic STS administration reduces the fraction of active platinum species (Table 5). Further research studies using sensitive ICP-MS approaches are needed to measure cisplatin levels in patients treated with and without STS.[71]

ONCOLOGIC SAFETY OF SYSTEMIC STS

Preclinical Studies

In small cell lung carcinoma (SCLC) cell lines, Muldoon et al[72] reported chemoprotection of cisplatin (15 μg/mL) and carboplatin (200 μg/mL) when STS (2,000 μg/mL) was administered concurrently, or 2-4 hours after administration (85%-95% live cells), compared with cell lines treated with cisplatin or carboplatin only (10%-20% live cells). However, when a broader time interval was studied, Dickey et al[50] found only very minimal protection (0%-10%) in cell lines treated with cisplatin (30-50 μM) and STS (8 g/m²) after 6-8 hours, which was similar compared with the cisplatin-only group. Another study also reported no difference in cell survival between neuroblastoma cell lines that received cisplatin with or without STS after 6 hours (0%-60%: $P > .05$).[68]

TABLE 3. Clinical Studies on the Otoprotective Effect of STS (without a control group)

Author, Year	Design	Patient Characteristics	Platinum Treatment	STS Specification	Audiometry	FU Time	Evaluable for HL	Hearing Function Outcomes	Adverse Events
Studies in adults									
Howell et al,[52] 1982	Phase I trial	17 patients with IP tumors Mean age: 52 years (31-65)	CIS IP dialysis over 4 hours; 6 courses Start at 90 mg/m^2, escalated to 270 mg/m^2	STS IV, over 12 hours 2.13 g/m^2 per hour Concurrent with CIS	PTA, unspecified	Post-Tx	5 patients	No HL observed	Increased serum creatinine, vomiting, hematologic toxicity, abdominal pain, decreased serum bicarbonate and potassium
Pfeifle et al,[56] 1985	Phase I trial	24 patients with different tumor types Median age: 56 years (15-73)	CIS IV over 2 hours 180-834 mg/m^2 1-3 courses	STS IV for 3 hours First hour 3.3 g/m^2, thereafter 9.9 g/m^2 Start 1 hour before CIS	PTA, unspecified	1 month post-Tx	5 complete courses	VIIIth nerve toxicity in 1 course at 225 mg/m^2 and 3 courses at 202.5 mg/m^2; not in 1 course at 180 mg/m^2 Incomplete courses: 8.4% with a change in hearing after Tx	Proteinuria, increased serum creatinine, hematuria, myelosuppression, nausea, vomiting, decreased serum magnesium levels
Markman et al,[55] 1990	Phase I trial	36 patients with solid tumors Median age: 56 years (25-72)	CIS IV over 2 hours 150-200 mg/m^2 1-6 courses	STS IV for 3 hours First hour 3.3 g/m^2, thereafter 6.6 g/m^2 Start 1 hour before CIS	PTA (0.25-20 kHz)	During Tx	22	55%: normal baseline at ≤8 kHz, of whom 58% developed HL in this range 45%: HL at 3-8 kHz at baseline; all showed continuous deterioration 77%: normal hearing at >8 kHz; all completely lost hearing in this range	Emesis, myelosuppression, increased creatinine, renal insufficiency, peripheral neuropathy
Reichman et al,[57] 1991	Phase II trial	11 patients with cervical cancer Median age: 43 years (25-57)	CIS IV over 2 hours 200 mg/m^2 2-5 courses	STS IV First hour 3.3 g/m^2, thereafter 6.6 g/m^2 Start 1 hour before CIS	PTA (1-20 kHz)	During Tx	9	44% HL at >8 kHz after 1 CIS course 77% mild-moderate HL at 8 kHz 55%: mild-moderate HL at 6 kHz 11%: mild-moderate HL at 1-4 kHz	Low Hb requiring red blood cell transfusion, nausea, vomiting, peripheral neuropathy, increased creatinine
Kim et al,[54] 1993	Phase I trial	28 patients with different tumor types Median age: 51 years (31-72)	CIS IV over 4 hours 180 mg/m^2 1 to ≥6 courses	STS IV over 6 hours First hour 4 g/m^2, thereafter 2 g/m^2 Concurrent with CIS	PTA (1-8 kHz)	During Tx	18	50% with HL 88% developed HL after course 1-2 Mostly at 4-8 kHz	Slight increase in serum creatinine, myelosuppression, nausea, vomiting, peripheral neuropathy
Madasu et al,[65] 1997	Inception cohort study	70 patients with HNSCC Mean age: 56 years EBRT (68-70 Gy)	CIS IA 150 mg/m^2 4 courses	STS IV Unspecified	PTA (0.25-4 kHz)	During Tx	49	25% HL after 1 course; 60% HL after 4 courses Mostly at 4-8 kHz	NA
Van Rijswijk et al,[58] 1997	Phase II trial	29 patients with ovarian cancer Median age: 54 years (23-72)	CIS IP over 6 hours 200 mg/m^2 1-6 courses	STS IP over 6 hours 4 g/m^2 as a bolus, followed by 12 g/m^2 Concurrent with CIS	PTA (0.25-8 kHz)	During Tx	23	35% with HL 75% had pre-existing HL that deteriorated (>15-30 dB) 25% developed new HL (drop of 15 dB in 1 ear; drop of >10 dB in 2 ears)	Intra-abdominal adhesions, inflow and outflow obstructions, septic peritonitis, ileus, nausea, vomiting, leukopenia, thrombocytopenia, increased creatinine
Balm et al,[51] 2004	Phase II trial	79 patients with HNSCC Mean age: 54 years (29-79) EBRT (70 Gy)	CIS IA 150 mg/m^2 4 courses	STS IV 9 g/m^2 over 30 minutes, followed by 12 g/m^2 over 2 hours	PTA, unspecified CTCAE	3 months post-Tx	79	10% reported HL grade 3 Results of audiometry not reported	Hematologic toxicities, mucositis, skin reactions, nausea, toxicity of the upper gastrointestinal tract, cardiotoxicity, treatment-related death, mucosal defect original tumor site, swallowing difficulties
Zuur et al,[59] 2007	Prospective cohort study	146 patients with HNSCC Median age: 54 years EBRT (70 Gy)	CIS IA 150 mg/m^2 4 courses	STS IV 9 g/m^2 over 30 minutes, followed by 12 g/m^2 over 2 hours	PTA (0.125-16 kHz)	During Tx and after a median of 7.5 weeks	Variable (range 141 before to 91 after Tx)	Largest HTL shifts after second and third CIS dose: average of 8 dB at 1-4 kHz and 24 dB at 8-12.5 kHz 59 ears (23%) under consideration for hearing aids	NA
Studies in children, adolescents, and young adults									
Neuwelt et al,[63] 2006	Phase I trial	12 patients with brain tumors Age: 17 months—12 years	CARBO IA 400 mg/m^2 in 2 days after BBBD 2-12 courses	STS IV 1 dose of 10-16 g/m^2 at 2 or 4 hours after CARBO; extra dose 4 hours after dose 1 in case of pre-existing HL	PTA (0.5-8 kHz)	During Tx	11	55% received STS at 4 hours (of whom 67% had pre-existing HL); 33% had HTLs of ≥40 dB at 2-8 kHz 45% received STS at 2 hours (no pre-existing HL), of whom 60% developed HL (≥40 dB at 2-8 kHz)	Increased sodium levels, myelosuppression, infection, cardiovascular toxicity, metabolic toxicity, gastrointestinal toxicity, neurologic toxicity, pulmonary toxicity, abdominal pain
Womack et al,[66] 2014	Retrospective data review	13 patients with IP tumors Mean age: 19 years (10-30)	Hyperthermic CIS IP 55-100 mg/m^2 1 course	STS IV over 12 hours Dose unknown Before, during, or 12 hours post-CIS	PTA (0.25-16 kHz)	2-15 months	13	46% with loss of 10-15 dB at one single frequency	NA
Harao et al,[64] 2020	Case report	9-year-old boy with MBL Craniospinal irradiation (23.4 Gy) + PF boost (32.4 Gy)	CIS IV 75 mg/m^2 8 courses	STS IV 16 g/m^2 At CIS course 6 and 7	PTA (1-8 kHz)	During Tx and after 12 months	—	At fifth cycle: HL up to ≥40 dB at 2-8 kHz At the end of seventh cycle: no deterioration of hearing After 12 months: ↓ HTLs at 2-8 kHz; 0.125-1 kHz within normal limits	NA

Abbreviations: BBBD, blood-brain barrier disruption; CARBO, carboplatin; CIS, cisplatin; CTCAE, Common Terminology Criteria for Adverse Events; EBRT, external-beam radiotherapy; FU, follow-up; HL, hearing loss; HNSCC, head and neck squamous cell carcinoma; HTL, hearing threshold level; IA, intra-arterial; IP, intra-peritoneal; IV, intravenous; MBL, medulloblastoma; NA, not assessed; PF, posterior fossa; PTA, pure tone audiometry; RCT, randomized controlled trial; STS, sodium thiosulfate; Tx, treatment.

TABLE 4. Preclinical Studies on the Pharmacokinetics of STS and Platinum

Author, Year	Study End Point	Species	Treatment Groups	Platinum Treatment	STS Specification	Samples	Evaluation Method	PK Results			
								C_{max}, μg/mL	AUC, μg-h/mL	$T_{1/2}$, Minutes	Elimination/Clearance
Saito et al,[67] 1997	Effect of STS on the PK of CIS	Guinea pig	10: CIS + STS concurrent + after 1 hour 14: CIS + STS at 3 and 6 hours 15: CIS only 8: STS only	CIS IM 7.5 mg/kg 3 injections 5-day interval	STS IP, 1,000 mg/kg; concurrent with CIS, and after 1, 3, and 6 hours	Blood (2-3 mL) perilymph (3-4 μL) at 1, 3, 6, and 24 hours	ICP-MS (FP and TP)	Plasma CIS + STS: 3.5 ± 1.0 CIS only: 1.9 ± 0.7 Perilymph CIS + STS: 0.4 ± 0.1 CIS only: 0.4 ± 0.1	NA	NA	Plasma Lower FP and TP concentrations in the CIS + STS group at 6 hours and 24 hours ($P < .05$) Perilymph Lower PT concentrations in the CIS + STS group at 24 hours ($P < .05$)
Muldoon et al,[48] 2000	Effect of STS on the PK of CARBO	Guinea pig	3: CARBO + STS 3: CARBO + saline	CARBO 24 mg/kg	STS 11.6 g/m^2 for 2 hours	Blood (0.5 mL each) at 5 minutes, 30 minutes, and 1-6 hours	AAS	Both groups: approximately 23.0 (range 15-29)	With STS: 60.7 ± 19.6 Without STS: 68.5 ± 21.5	NA	CARBO clearance With STS: 208 ± 51 mL/h/kg Without STS: 184 ± 44 mL/h/kg ($P = .33$)
Harned et al,[68] 2008	PK of STS	Mouse	6: STS only	—	STS IP 3.5 g/kg	Blood at 1 and 15 minutes after injection	Methylene blue test	1 minute: 1,717 ± 345 5 minutes: 8,598 ± 493	NA	NA	NA
	Effect of STS on the PK of CIS	Mouse	8: CIS + STS 2: CIS only	CIS IP 4 mg/kg total per day for 4 days	STS IP 3.5 g/k total per day concurrently with CIS	Blood at 15 minutes, 45 minutes, 1 hour, and 6 hours	AAS		NA	NA	CIS concentrations after 6 hours did not differ between groups (no data)
Pierre et al,[69] 2009	PK of STS	Guinea pig	10: STS only 2: saline	—	STS IV 103 mg/kg as a bolus injection	Perilymph (1 μL) and blood (0.35 mL) after 10 and 30 minutes; 1, 2, and 3 hours	HPLC	Perilymph: approximately 60 μM Plasma: approximately 300 μM	Perilymph: 51.7 Plasma: 105	Perilymph: 50 Plasma: 20	Perilymph mean STS concentrations at 200 min: approximately 6 μg/ml Plasma mean STS concentrations at 200 minutes: approximately 1.5 μg/mL

Abbreviations: AAS, atomic absorption spectrometry; AUC, area under the plasma drug concentration-time curve; CARBO, carboplatin; CIS, cisplatin; C_{max}, peak plasma concentration of the drug after administration; FP, free platinum; HPLC, high-performance liquid chromatography; ICP-MS, inductively coupled mass spectrometry; IM, intra-muscular; IP, intraperitoneal; IV, intravenous; NA, not assessed; PK, pharmacokinetics; PT, platinum; STS, sodium thiosulfate; TP, total platinum; Tx, treatment; $T_{1/2}$, time required for the concentration of the drug to reach half of its original value.

TABLE 5. Clinical Studies on the Pharmacokinetics of STS and Platinum

Author, Year	Study End Point	Patient Characteristics	STS Group	Comparison Group	Platinum Treatment	STS Specification	Samples	Evaluation Method	PK Results			
									C_{max}, μg/mL	AUC, μg-h/mL	$T_{1/2}$, Minutes	Elimination/ Clearance
Howell et al,[52] 1982	Effect of STS on the PK of CIS	IP tumors Mean age: 52 years (31-65)	17: CIS + STS	—	CIS IP dialysis over 4 hours 6 courses 90-270 mg/m^2	STS IV, over 12 hours 2.13 g/m^2 per hour Concurrent with CIS	Blood + peritoneal dialysate (every 60 minutes after CIS)	HPLC (FP)	Plasma: 7.5 PC: 85 No effect of STS (P > .05)	Plasma: 7.2 ± 5.5 PC: 97.1 ± 64.9 Addition of STS: 2.9- and 1.9-fold increase (P < .01)[a]	Plasma: 50-66 PC: 51-53 No effect of STS (P > .05)	Plasma + PC Exponential decrease in CIS concentrations over time
Pfeifle et al,[56] 1985	Effect of STS on the PK of CIS	Different tumor types Median age: 56 years (15-73)	6: CIS + STS	5: CIS only	CIS + STS: IV 202.5 mg/m^2 7 courses CIS only: IV 100 mg/m^2 8 courses	STS IV for 3 hours First hour 3.3 g/m^2, thereafter 9.9 g/m^2 Start 1 hour before CIS	Blood (22 time points up to 7 hours after CIS)	HPLC	With STS 6.9 Without STS: 3.2	With STS: 17.1 Without STS: 8.3	With STS: 36.5 Without STS: 38.5	Elimination rate With STS: 0.019 min/L Without STS: 0.018 min/L Clearance level With STS: 222 mL/min/m^2 Without STS 234 mL/min/m^2
Goel et al,[70] 1989	Effect of STS on the PK of CIS	IP tumors Mean age: 59 years (29-57)	14: CIS + STS	—	CIS IP 90 mg/m^2 5 courses	STS IV in a bolus of 4 g/m^2 before CIS, followed by 12 g/m^2 over 6 hours	Blood + peritoneal dialysate (20 time points up to 24 hours after CIS)	HPLC	NA	Plasma With STS: 6.7 ± 2.2 Without STS: 8.8 ± 3.8: P < .05[b] PC With STS: 96.5 ± 54.4 Without STS: 149 ± 38.0: P < .05	Plasma: 80 ± 65 PC: 72 ± 59	Plasma clearance level: 59 ± 52 mL/min
Neuwelt et al,[62] 1998	PK of STS in the presence of CARBO	Brain tumors Age: 2-68 years	25: CARBO + STS 4-16 g/m^2 8: CARBO + STS 20 g/m^2	—	CARBO IA over 10 minutes 400 mg/m^2 per month 4-12 courses	STS IV over 15 minutes 4-20 g/m^2 2 hours after CARBO	Blood + urine (directly after STS injection, after 15 minutes, and after 24 hours)	Methylene blue test	Plasma (20 mg/m^2) End bolus: 33.1 Urine (20 mg/m^2) 15 minutes after bolus: 198.1	NA	NA	STS levels not detectable at 24 hours post-Tx

Abbreviations: AUC, area under the plasma drug concentration-time curve; BL, bilateral; CARBO, carboplatin; CIS, cisplatin; C_{max}, peak plasma concentration of a drug after administration; FP, free platinum; HPLC, high-performance liquid chromatography; IA, intra-arterial; IP, intraperitoneal; IV, intravenous; NA, not assessed; PC, peritoneal cavity; PK, pharmacokinetics; PT, platinum; STS, sodium thiosulfate; TP, total platinum; Tx, treatment; $T_{1/2}$, time required for the concentration of the drug to reach half of its original value; UL, unilateral.

[a]When the peritoneum to plasma AUC ratio was calculated separately for each patient, no variation in this ratio with dose was observed (P > .05: mean ratio for all cisplatin courses 12.4 [range 2.9-37.4]).

[b]Significant difference only for the last 3 hours of exposure where a reduction of 54% was observed (P < .05).

TABLE 6. Preclinical Studies on the Effect of STS on Platinum Antitumor Efficacy

Author, Year	Species	Treatment Groups	Platinum Treatment	STS Specification	Evaluation Method	Results		*P*
						With STS	Without STS	
Muldoon et al,[48] 2000	Rat with LX-1 human SCLC xenograft	8: CARBO + STS at 2 and 6 hours 8: CARBO + STS at 8 hours 20: CARBO only 20: no Tx	CARBO 200 mg/m^2	STS 8 g/m^2 at 2, 6 or 8 hours after CARBO	Time to tumor progression	STS 2 hours and 6 hours: 6.4 ± 0.8 days STS 8 hours group: 8.1 ± 0.7 days	CARBO only: 8.9 ± 0.6 days	.012 .188
Muldoon et al,[72] 2001	SCLC cell line + human fibroblast cell strain	CARBO + STS CIS + STS CIS or CARBO only	CARBO 200 μg/mL CIS 15 μg/mL	STS 2,000 μg/mL: immediately, 2 hours, or 4 hours after PT	Live cell number by using CPA kit	CIS + STS immediately, at 2 hours, or 4 hours: 90%-95% live cells CARBO + STS immediately, at 2 hours, or 4 hours: 85%-90% live cells	CIS only: 10% live cells CARBO only: 20% live cells	NA
Neuwelt et al,[73] 2004	Rat with LX-1 human SCLC xenograft	8: CARBO + STS 8: CARBO only 8: no Tx	CARBO 200 mg/m^2	STS IV 8 g/m^2 at 4 or 8 hours after CARBO	Tumor volume	CARBO + STS: 3.7 ± 0.6 mm^3	CARBO only: 4.3 ± 1.0 mm^3 Untreated: 29.1 ± 4.1 mm^3	<.0001 (all groups)
Dickey et al,[50] 2005	Human GBL, OC, MBL and SCLC cell lines	CIS + or - STS	CIS 30-50 μM	STS IV 8 g/m^2 0, 2, 4, 6 or 8 hours after CIS	Cell viability and immunoblotting assays	CIS + STS: 70%-100% protection of cells up to 2 hours after CIS; 30%-45% at 4 hours; 0%-10% at 6-8 hours post-CIS	CIS only: reduction in cell viability of 58% (GBL cells), 81% (OC cells), and 100% (MBDL and SCLC cells)	NA
Harned et al,[68] 2008	Human NBL cell lines	6: CIS + or - STS	CIS 0-2 μg/mL	STS 0.5-1.0 mg/mL at 0 or 6 hours after CIS	Cytotoxicity by using FDIMA	CIS + STS concurrently (5/6): survival fraction of cells 70%-100% CIS + STS after 6h (5/6): survival fraction of cells 0%-60%	CIS only (5/6): survival fraction of cells 0%-60%	<.05 >.05
	Mouse with NBL xenografts	6: CIS + STS concurrently 6: CIS + STS after 6 hours 6: CIS only 6: no Tx	CIS IP 4 mg/kg total per day 4 days	STS IP 3.5 g/k total per day concurrently with CIS or after 6 hours 4 days	Tumor volume + time to tumor progression	Tumor volume CIS + STS concurrently: 1,400 mm^3 CIS + STS after 6 hours: max. 800 mm^3 Tumor progression CIS + STS concurrently: 20 days CIS + STS after 6 hours: 210 days	Tumor volume CIS only: max. 800 mm^3 Tumor progression CIS only: 210 days	<.05 >.05 .03 .90

Abbreviations: CIS, cisplatin; CPA, cell proliferation assay; FDIMA, fluorescence/digital imaging microscopy assay; GBL, glioblastoma; IP, intraperitoneal; IV, intravenous; MBL, medulloblastoma; NA, not assessed; NBL, neuroblastoma; OC, ovarian carcinoma; PT, platinum; SCLC, small cell lung carcinoma; STS, sodium thiosulfate; Tx, treatment.

Furthermore, Neuwelt et al[73] studied tumor volume (TV) in rats with LX-1 human SCLC xenografts. TV of untreated rats was approximately 29 mm^3 (n = 8), approximately 4.3 mm^3 for rats treated with carboplatin (200 mg/m^2: n = 8), and approximately 3.7 mm^3 for rats that received systemic IV STS (8 g/m^2: n = 8) at 4-8 hours ($P < .0001$; all groups).[73] In another study, mice were treated with IP cisplatin only (4 mg/kg total per day for 4 days: n = 6) or with IP cisplatin and STS (3.5 g/kg total per day: n = 6). For mice treated with STS after 6 hours, TV was max 800 mm^3 ($P > .05$); for the mice treated with STS and cisplatin at the same time (n = 6), this was 1,400 mm^3 ($P < .05$). In addition, within these mice, the time to tumor progression was also similar between the cisplatin only and STS-at-6-hours group (210 days, $P = .9$), but shorter for the group that received cisplatin and STS concomitantly (20 days, $P = .03$).[68] In a similar designed study with carboplatin (200 mg/m^2) and STS, comparable findings were reported.[48]

The studies described above indicate that the delayed administration of STS at 6 hours after cisplatin does not reduce the impact of cisplatin on tumor growth and cell survival. A similar conclusion from delayed STS and carboplatin is difficult to draw from these data (Table 6).

Clinical Studies

In children with standard-risk hepatoblastoma, Brock et al[40] reported that event-free survival (EFS) and overall survival (OS) were similar between the IV STS group (EFS, 82% [95% CI, 69 to 90]; OS, 98% [95% CI, 88 to 100]) and the non-STS group (EFS, 79% [95% CI, 65 to 88]; OS, 92% [95% CI, 81 to 97])[40] at a median follow-up time of 3 years. In children with any tumor type at a similar follow-up time, Freyer et al[41] reported no difference between the IV STS group and controls regarding EFS and OS ($P = .36$ and .07, respectively). Although there was no evidence of a tumor-protective effect from STS in the whole cohort, a post hoc analysis confirmed no effect in 77 patients with localized disease (EFS and OS: $P = .73$ and .88, respectively) but revealed a survival difference in OS in 47 patients with disseminated disease in the STS-treated group ($P = .009$; relative hazard ratio, 4.10 [95% CI, 1.30 to 12.97]).[41] In a subsequent follow-up paper, the same authors (2022) noted that the children with disseminated disease who did not receive STS had a better than originally predicted survival (compared with the literature) and that the difference between the two arms was most probably related to an imbalance in prognostic groups.[74]

In conclusion, systemic STS is safe to administer in children with localized disease (Table 2). For now, STS is not approved for use in those with metastatic disease, although a biologically plausible rationale is lacking for why a 6-hour delay in STS administration after cisplatin infusion would lead to reduced antitumor efficacy.[75]

FUTURE PERSPECTIVES

The STS compound used in the pediatric RCTs has recently been licensed by the FDA (Pedmark) and EMA and MHRA (Pedmarqsi), and is ready for implementation into current practice in children with cancers requiring cisplatin therapy. These include mainly neuroblastoma, hepatoblastoma, nasopharyngeal carcinoma, osteosarcoma, medulloblastoma, germ cell tumors, and rarely other cancers. A guideline published prelicensing, however, recommends it for use in children with standard-risk hepatoblastoma only.[76] This guideline therefore requires a postlicensing update. To study the efficacy and safety of STS in metastatic disease, specific tumor diagnoses RCTs or single-arm trials for which adequately available historic outcomes are needed. Preferably, these studies should be supported by biologic and imaging studies to assess both otoprotection and treatment response in the presence of properly administered (delayed) STS.

Second, more PK studies are needed to understand the effect of STS on cisplatin kinetics, including measurement of unbound cisplatin and carboplatin. This contrasts to the approach taken in the majority of published studies in this area, in which total plasma platinum is most commonly measured (including aqua complexes and STS-bound platinum). Evaluating platinum in ultrafiltrate samples would provide a measure of free drug levels, which are more likely to correlate with clinical response and toxicity.[77,78] Using this method would also be beneficial to confirm the safety of STS when administered 6 hours after the end of cisplatin infusion, as previously suggested.[48,50,68] An effort is currently ongoing to study relationships between cisplatin PK, pharmacogenomics, and biomarkers of toxicity, as well as clinical efficacy and toxicity in the PHITT Trial (ISRCTN17869351).[79]

Third, to administer STS in the appropriate window to obtain otoprotection, cisplatin infusion durations require reduction to a maximum of 6 hours. In Europe, cisplatin is sometimes administered as a 24- to 96-hour infusion, historically implemented to reduce emesis.[80,81] However, there is no evidence that longer infusion durations are more effective in terms of antitumor effect compared with shorter durations. Specifically, in the SIOPEL 6 trial, the infusion of cisplatin was reduced from 48 to 6 hours, with no difference in survival outcome when compared with SIOPEL 3.[82] In addition, there is no evidence that a single dose of cisplatin is more effective compared with split, daily doses. The latter has been used for patients with germ cell tumors for several decades (ie, 20 mg/m^2 for 5 days per cycle), and has shown to result in excellent survival rates.[83,84] For future studies, it would therefore be important to design them, with the reduced cisplatin infusion duration and the use of split doses in specific tumor groups, thereby powering the study appropriately, to allow outcome analyses, similar to the previous RCTs in children.

Fourth, there is preliminary evidence from early-phase adult studies that hearing loss deterioration already starts after the first dose of cisplatin and may worsen thereafter with time, independent of other treatments.[55,58,64] This implies that it is important to administer STS alongside the first cisplatin cycle of treatment, as it may be detrimental to wait to give STS after hearing loss has already developed. Whether STS may prevent subsequent additional hearing loss, after the onset of CIHL, upon cisplatin rechallenge, is not well understood. A current trial is under way to assess this phenomenon in children with relapsed or refractory hepatoblastoma (ClinicalTrials.gov identifier: NCT05756660).[85]

Fifth, historically, STS was often administered concomitantly with cisplatin, either to allow the infusion of higher doses of cisplatin or to reduce the development of side effects, including nephrotoxicity.[51-60,66] It should be noted that when STS is given for otoprotection at 6 hours after the end of cisplatin, it is unlikely to reduce nephrotoxicity that occurs earlier than ototoxicity. It is therefore important that the currently approved form of high-dose STS in children is not provided with a view to protecting renal function, but only for otoprotection.[42]

Sixth, future investigation on the potential for STS to prevent CIHL from carboplatin is justified. This may be challenging to achieve in the short term. The PK of the activation reaction distinguishes the two drugs from each other. Cisplatin will already be deactivated systemically after 6 hours, but carboplatin is more chemically stable.[77,86] Thus, administering STS after 6 hours would generate a risk of deactivating the carboplatin and negatively affecting its antitumor efficacy. Carefully planned PK and xenograft studies are therefore necessary to determine an appropriate time window for STS administration after carboplatin infusion.

Seventh, it is important to highlight the variations in audiologic testing and end point definitions among the clinical studies reviewed, taking into consideration differences in test frequency range, ototoxicity definitions, and consistency in hearing endpoints. For example, Brock et al[40] used the Brock scale, whereas Freyer et al[41] used the ASHA criteria. Clemens et al[2] concluded that there is good concordance between ototoxicity grading scales; however, severity definitions and intermediate grades diverge. Acknowledging these differences, a recent reevaluation of ACCL0431 with as end point the SIOP ototoxicity criteria revealed a lower incidence of grade ≥2 CIHL in the STS arm compared with the observation arm (3/58 [5.2%] and 18/63 [28.6%], respectively).[87] This underscores the need for careful consideration of the type of hearing assessment and ototoxicity grading scale used when interpreting the prevalence of hearing loss in studies. Consequently, we suggest incorporating age-dependent audiologic testing, as recommended by Meijer et al,[88] and the SIOP ototoxicity grading scale, to facilitate uniform outcomes regarding platinum-induced hearing loss.[89]

In conclusion, systemic administration of STS effectively reduces the development of CIHL in both the preclinical and clinical settings. It has been shown to be safe, in children with localized disease, when a window of 6 hours is respected. Even if hearing loss develops, its severity is reduced. More well-executed studies on the PK and safety of STS and cisplatin are needed, especially in patients with metastatic disease. In the future, this will hopefully lead to STS otoprotection becoming standard of care for all cisplatin-treated patients with cancer, thereby decreasing the debilitating impact of CIHL, on speech development, social isolation, neurocognitive development, and consequent QoL, as well as reducing the risk of late sequelae, such as early dementia later in life.

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REFERENCES

1. Al-Khatib T, Cohen N, Carret AS, et al: Cisplatinum ototoxicity in children, long-term follow up. Int J Pediatr Otorhinolaryngol 74:913-919, 2010
2. Clemens E, Brooks B, de Vries ACH, et al: A comparison of the Muenster, SIOP Boston, Brock, Chang and CTCAEv4.03 ototoxicity grading scales applied to 3,799 audiograms of childhood cancer patients treated with platinum-based chemotherapy. PLoS One 14:e0210646, 2019
3. Knight KR, Chen L, Freyer D, et al: Group-wide, prospective study of ototoxicity assessment in children receiving cisplatin chemotherapy (ACCL05C1): A report from the Children's Oncology Group. J Clin Oncol 35:440-445, 2017
4. Kushner BH, Budnick A, Kramer K, et al: Ototoxicity from high-dose use of platinum compounds in patients with neuroblastoma. Cancer 107:417-422, 2006
5. Nitz A, Kontopantelis E, Bielack S, et al: Prospective evaluation of cisplatin- and carboplatin-mediated ototoxicity in paediatric and adult soft tissue and osteosarcoma patients. Oncol Lett 5: 311-315, 2013
6. Peleva E, Emami N, Alzahrani M, et al: Incidence of platinum-induced ototoxicity in pediatric patients in Quebec. Pediatr Blood Cancer 61:2012-2017, 2014
7. Gentilin E, Simoni E, Candito M, et al: Cisplatin-induced ototoxicity: Updates on molecular targets. Trends Mol Med 25:1123-1132, 2019
8. Sheth S, Mukherjea D, Rybak LP, et al: Mechanisms of cisplatin-induced ototoxicity and otoprotection. Front Cell Neurosci 11:338, 2017
9. Lambert MP, Shields C, Meadows AT: A retrospective review of hearing in children with retinoblastoma treated with carboplatin-based chemotherapy. Pediatr Blood Cancer 50:223-226, 2008
10. Smits C, Swen SJ, Theo Goverts S, et al: Assessment of hearing in very young children receiving carboplatin for retinoblastoma. Eur J Cancer 42:492-500, 2006
11. Musial-Bright L, Fengler R, Henze G, et al: Carboplatin and ototoxicity: Hearing loss rates among survivors of childhood medulloblastoma. Childs Nerv Syst 27:407-413, 2011
12. Qaddoumi I, Bass JK, Wu J, et al: Carboplatin-associated ototoxicity in children with retinoblastoma. J Clin Oncol 30:1034-1041, 2012
13. Clemens E, de Vries AC, Pluijm SF, et al: Determinants of ototoxicity in 451 platinum-treated Dutch survivors of childhood cancer: A DCOG late-effects study. Eur J Cancer 69:77-85, 2016
14. Soliman SE, D'Silva CN, Dimaras H, et al: Clinical and genetic associations for carboplatin-related ototoxicity in children treated for retinoblastoma: A retrospective noncomparative single-institute experience. Pediatr Blood Cancer 65:e26931, 2018
15. Landier W, Knight K, Wong FL, et al: Ototoxicity in children with high-risk neuroblastoma: Prevalence, risk factors, and concordance of grading scales—A report from the Children's Oncology Group. J Clin Oncol 32:527-534, 2014
16. Meijer AJM, Li KH, Brooks B, et al: The cumulative incidence of cisplatin-induced hearing loss in young children is higher and develops at an early stage during therapy compared with older children based on 2052 audiological assessments. Cancer 128:169-179, 2022
17. Moke DJ, Luo C, Millstein J, et al: Prevalence and risk factors for cisplatin-induced hearing loss in children, adolescents, and young adults: A multi-institutional North American cohort study. Lancet Child Adolesc Health 5:274-283, 2021
18. Bass JK, Hua CH, Huang J, et al: Hearing loss in patients who received cranial radiation therapy for childhood cancer. J Clin Oncol 34:1248-1255, 2016
19. Ghazwani Y, Qaddoumi I, Bass JK, et al: Profound hearing loss following surgery in pediatric patients with posterior fossa low-grade glioma. Neurooncol Pract 5:96-103, 2018
20. Clemens E, van der Kooi ALF, Broer L, et al: The influence of genetic variation on late toxicities in childhood cancer survivors: A review. Crit Rev Oncol Hematol 126:154-167, 2018
21. Einarsson EJ, Petersen H, Wiebe T, et al: Severe difficulties with word recognition in noise after platinum chemotherapy in childhood, and improvements with open-fitting hearing-aids. Int J Audiol 50:642-651, 2011
22. Gurney JG, Tersak JM, Ness KK, et al: Hearing loss, quality of life, and academic problems in long-term neuroblastoma survivors: A report from the Children's Oncology Group. Pediatrics 120: e1229-e1236, 2007
23. Bass JK, Liu W, Banerjee P, et al: Association of hearing impairment with neurocognition in survivors of childhood cancer. JAMA Oncol 6:1363-1371, 2020
24. Rajput K, Edwards L, Brock P, et al: Ototoxicity-induced hearing loss and quality of life in survivors of paediatric cancer. Int J Pediatr Otorhinolaryngol 138:110401, 2020
25. Golub JS, Brickman AM, Ciarleglio AJ, et al: Association of subclinical hearing loss with cognitive performance. JAMA Otolaryngol Head Neck Surg 146:57-67, 2020
26. Jiang F, Mishra SR, Shrestha N, et al: Association between hearing aid use and all-cause and cause-specific dementia: An analysis of the UK Biobank cohort. Lancet Public Health 8:e329-e338, 2023
27. Chern A, Sharma RK, Golub JS: Hearing loss and incident dementia: Claims data from the New York SPARCS Database. Otol Neurotol 43:36-41, 2022
28. Hendriks S, Ranson JM, Peetoom K, et al: Risk factors for young-onset dementia in the UK Biobank. JAMA Neurol 81:134-142, 2024
29. Dawes P, Völter C: Do hearing loss interventions prevent dementia? Z Gerontol Geriatr 56:261-268, 2023
30. Wayne RV, Johnsrude IS: A review of causal mechanisms underlying the link between age-related hearing loss and cognitive decline. Ageing Res Rev 23:154-166, 2015
31. Dawes P, Emsley R, Cruickshanks KJ, et al: Hearing loss and cognition: The role of hearing AIDS, social isolation and depression. PLoS One 10:e0119616, 2015
32. van Atteveld JE, de Winter DTC, Pluimakers VG, et al: Frailty and sarcopenia within the earliest national Dutch childhood cancer survivor cohort (DCCSS-LATER): A cross-sectional study. Lancet Healthy Longev 4:e155-e165, 2023
33. Geenen MM, Cardous-Ubbink MC, Kremer LC, et al: Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. JAMA 297:2705-2715, 2007
34. van Erp LME, Maurice-Stam H, Kremer LCM, et al: Health-related quality of life in Dutch adult survivors of childhood cancer: A nation-wide cohort study. Eur J Cancer 152:204-214, 2021
35. Lee JW, Pussegoda K, Rassekh SR, et al: Clinical practice recommendations for the management and prevention of cisplatin-induced hearing loss using pharmacogenetic markers. Ther Drug Monit 38:423-431, 2016
36. Sooriyaarachchi M, George GN, Pickering IJ, et al: Tuning the metabolism of the anticancer drug cisplatin with chemoprotective agents to improve its safety and efficacy. Metallomics 8: 1170-1176, 2016
37. Bijarnia RK, Bachtler M, Chandak PG, et al: Sodium thiosulfate ameliorates oxidative stress and preserves renal function in hyperoxaluric rats. PLoS One 10:e0124881, 2015
38. Yu D, Gu J, Chen Y, et al: Current strategies to combat cisplatin-induced ototoxicity. Front Pharmacol 11:999, 2020
39. Hazlitt RA, Min J, Zuo J: Progress in the development of preventative drugs for cisplatin-induced hearing loss. J Med Chem 61:5512-5524, 2018
40. Brock PR, Maibach R, Childs M, et al: Sodium thiosulfate for protection from cisplatin-induced hearing loss. N Engl J Med 378:2376-2385, 2018

41. Freyer DR, Chen L, Krailo MD, et al: Effects of sodium thiosulfate versus observation on development of cisplatin-induced hearing loss in children with cancer (ACCL0431): A multicentre, randomised, controlled, open-label, phase 3 trial. Lancet Oncol 18:63-74, 2017
42. Dhillon S: Sodium thiosulfate: Pediatric first approval. Paediatr Drugs 25:239-244, 2022
43. Orgel E, Freyer DR, Ullrich NJ, et al: Assessment of provider perspectives on otoprotection research for children and adolescents: A Children's Oncology Group Cancer Control and Supportive Care Committee survey. Pediatr Blood Cancer 67:e28647, 2020
44. Otto WC, Brown RD, Gage-White L, et al: Effects of cisplatin and thiosulfate upon auditory brainstem responses of Guinea pigs. Hear Res 35:79-85, 1988
45. Church MW, Kaltenbach JA, Blakley BW, et al: The comparative effects of sodium thiosulfate, diethyldithiocarbamate, fosfomycin and WR-2721 on ameliorating cisplatin-induced ototoxicity. Hear Res 86:195-203, 1995
46. Neuwelt EA, Brummett RE, Remsen LG, et al: In vitro and animal studies of sodium thiosulfate as a potential chemoprotectant against carboplatin-induced ototoxicity. Cancer Res 56:706-709, 1996
47. Kaltenbach JA, Church MW, Blakley BW, et al: Comparison of five agents in protecting the cochlea against the ototoxic effects of cisplatin in the hamster. Otolaryngol Head Neck Surg 117:493-500, 1997
48. Muldoon LL, Pagel MA, Kroll RA, et al: Delayed administration of sodium thiosulfate in animal models reduces platinum ototoxicity without reduction of antitumor activity. Clin Cancer Res 6: 309-315, 2000
49. Videhult Pierre P, Haglöf J, Linder B, et al: Cisplatin-induced metabolome changes in serum: An experimental approach to identify markers for ototoxicity. Acta Otolaryngol 137:1024-1030, 2017
50. Dickey DT, Wu YJ, Muldoon LL, et al: Protection against cisplatin-induced toxicities by N-acetylcysteine and sodium thiosulfate as assessed at the molecular, cellular, and in vivo levels. J Pharmacol Exp Ther 314:1052-1058, 2005
51. Balm AJ, Rasch CR, Schornagel JH, et al: High-dose superselective intra-arterial cisplatin and concomitant radiation (RADPLAT) for advanced head and neck cancer. Head Neck 26:485-493, 2004
52. Howell SB, Pfeifle CL, Wung WE, et al: Intraperitoneal cisplatin with systemic thiosulfate protection. Ann Intern Med 97:845-851, 1982
53. Ishikawa E, Sugimoto H, Hatano M, et al: Protective effects of sodium thiosulfate for cisplatin-mediated ototoxicity in patients with head and neck cancer. Acta Otolaryngol 135:919-924, 2015
54. Kim S, Howell SB, McClay E, et al: Dose intensification of cisplatin chemotherapy through biweekly administration. Ann Oncol 4:221-227, 1993
55. Markman M, D'Acquisto R, Iannotti N, et al: Phase-1 trial of high-dose intravenous cisplatin with simultaneous intravenous sodium thiosulfate. J Cancer Res Clin Oncol 117:151-155, 1991
56. Pfeifle CE, Howell SB, Felthouse RD, et al: High-dose cisplatin with sodium thiosulfate protection. J Clin Oncol 3:237-244, 1985
57. Reichman B, Markman M, Hakes T, et al: Phase II trial of high-dose cisplatin with sodium thiosulfate nephroprotection in patients with advanced carcinoma of the uterine cervix previously untreated with chemotherapy. Gynecol Oncol 43:159-163, 1991
58. van Rijswijk RE, Hoekman K, Burger CW, et al: Experience with intraperitoneal cisplatin and etoposide and i.v. sodium thiosulphate protection in ovarian cancer patients with either pathologically complete response or minimal residual disease. Ann Oncol 8:1235-1241, 1997
59. Zuur CL, Simis YJ, Lansdaal PE, et al: Risk factors of ototoxicity after cisplatin-based chemo-irradiation in patients with locally advanced head-and-neck cancer: A multivariate analysis. Int J Radiat Oncol Biol Phys 68:1320-1325, 2007
60. Zuur CL, Simis YJ, Lansdaal PE, et al: Ototoxicity in a randomized phase III trial of intra-arterial compared with intravenous cisplatin chemoradiation in patients with locally advanced head and neck cancer. J Clin Oncol 25:3759-3765, 2007
61. Doolittle ND, Muldoon LL, Brummett RE, et al: Delayed sodium thiosulfate as an otoprotectant against carboplatin-induced hearing loss in patients with malignant brain tumors. Clin Cancer Res 7: 493-500, 2001
62. Neuwelt EA, Brummett RE, Doolittle ND, et al: First evidence of otoprotection against carboplatin-induced hearing loss with a two-compartment system in patients with central nervous system malignancy using sodium thiosulfate. J Pharmacol Exp Ther 286:77-84, 1998
63. Neuwelt EA, Gilmer-Knight K, Lacy C, et al: Toxicity profile of delayed high dose sodium thiosulfate in children treated with carboplatin in conjunction with blood-brain-barrier disruption. Pediatr Blood Cancer 47:174-182, 2006
64. Harao T, Yamada A, Kinoshita M, et al: Prevention of cisplatin-induced hearing-loss by sodium thiosulfate in medulloblastoma. Pediatr Int 62:1204-1206, 2020
65. Madasu R, Ruckenstein MJ, Leake F, et al: Ototoxic effects of supradose cisplatin with sodium thiosulfate neutralization in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg 123:978-981, 1997
66. Womack AM, Hayes-Jordan A, Pratihar R, et al: Evaluation of ototoxicity in patients treated with hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin and sodium thiosulfate. Ear Hear 35:e243-e247, 2014
67. Saito T, Zhang ZJ, Manabe Y, et al: The effect of sodium thiosulfate on ototoxicity and pharmacokinetics after cisplatin treatment in Guinea pigs. Eur Arch Otorhinolaryngol 254:281-286, 1997
68. Harned TM, Kalous O, Neuwelt A, et al: Sodium thiosulfate administered six hours after cisplatin does not compromise antineuroblastoma activity. Clin Cancer Res 14:533-540, 2008
69. Pierre PV, Engmér C, Wallin I, et al: High concentrations of thiosulfate in scala tympani perilymph after systemic administration in the Guinea pig. Acta Otolaryngol 129:132-137, 2009
70. Goel R, Cleary SM, Horton C, et al: Effect of sodium thiosulfate on the pharmacokinetics and toxicity of cisplatin. J Natl Cancer Inst 81:1552-1560, 1989
71. Brouwers EE, Tibben MM, Rosing H, et al: Sensitive inductively coupled plasma mass spectrometry assay for the determination of platinum originating from cisplatin, carboplatin, and oxaliplatin in human plasma ultrafiltrate. J Mass Spectrom 41:1186-1194, 2006
72. Muldoon LL, Walker-Rosenfeld SL, Hale C, et al: Rescue from enhanced alkylator-induced cell death with low molecular weight sulfur-containing chemoprotectants. J Pharmacol Exp Ther 296: 797-805, 2001
73. Neuwelt EA, Pagel MA, Kraemer DF, et al: Bone marrow chemoprotection without compromise of chemotherapy efficacy in a rat brain tumor model. J Pharmacol Exp Ther 309:594-599, 2004
74. Orgel E, Villaluna D, Krailo MD, et al: Sodium thiosulfate for prevention of cisplatin-induced hearing loss: Updated survival from ACCL0431. Lancet Oncol 23:570-572, 2022
75. Brock P, Meijer A, Kogner P, et al: Sodium thiosulfate as cisplatin otoprotectant in children: The challenge of when to use it. Pediatr Blood Cancer 70:e30248, 2023
76. Freyer DR, Brock PR, Chang KW, et al: Prevention of cisplatin-induced ototoxicity in children and adolescents with cancer: A clinical practice guideline. Lancet Child Adolesc Health 4:141-150, 2020
77. Qin Z, Ren G, Yuan J, et al: Systemic evaluation on the pharmacokinetics of platinum-based anticancer drugs from animal to cell level: Based on total platinum and intact drugs. Front Pharmacol 10:1485, 2019
78. Brouwers EE, Tibben M, Rosing H, et al: The application of inductively coupled plasma mass spectrometry in clinical pharmacological oncology research. Mass Spectrom Rev 27:67-100, 2008
79. University of Birmingham: Paediatric Hepatic International Tumour Trial. PHITT, 2017. https://www.birmingham.ac.uk/Documents/college-mds/trials/crctu/phitt/Protocol/Current/PHITT-Protocol-version-3-0-17Oct2018.pdf
80. Jordan NS, Schauer PK, Schauer A, et al: The effect of administration rate on cisplatin-induced emesis. J Clin Oncol 3:559-561, 1985
81. Jacobs C, Bertino JR, Goffinet DR, et al: 24-hour infusion of cis-platinum in head and neck cancers. Cancer 42:2135-2140, 1978
82. Maibach R, Childs M, Rajput K, et al: SIOPEL 6: A multicenter open-label randomized phase III trial of the efficacy of sodium thiosulphate (STS) in reducing ototoxicity in patients receiving cisplatin (Cis) monotherapy for standard-risk hepatoblastoma (SR-HB). J Clin Oncol 32, 2014 (suppl; abstr TPS10094)
83. Grimison PS, Stockler MR, Thomson DB, et al: Comparison of two standard chemotherapy regimens for good-prognosis germ cell tumors: Updated analysis of a randomized trial. J Natl Cancer Inst 102:1253-1262, 2010
84. Funt SA, McHugh DJ, Tsai S, et al: Four cycles of etoposide plus cisplatin for patients with good-risk advanced germ cell tumors. Oncologist 26:483-491, 2021
85. Children's Hospital Medical Center Cincinnati: Sodium Thiosulfate Otoprotection During Salvage Cisplatin Therapy, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT05756660
86. Terheggen PM, Begg AC, Emondt JY, et al: Formation of interaction products of carboplatin with DNA in vitro and in cancer patients. Br J Cancer 63:195-200, 1991
87. Orgel E, Knight KR, Villaluna D, et al: Reevaluation of sodium thiosulfate otoprotection using the consensus International Society of Paediatric Oncology Ototoxicity Scale: A report from the Children's Oncology Group study ACCL0431. Pediatr Blood Cancer 70:e30550, 2023
88. Meijer AJM, van den Heuvel-Eibrink MM, Brooks B, et al: Recommendations for age-appropriate testing, timing, and frequency of audiologic Monitoring during childhood cancer treatment: An International Society of Paediatric Oncology Supportive Care Consensus Report. JAMA Oncol 7:1550-1558, 2021
89. Brock PR, Knight KR, Freyer DR, et al: Platinum-induced ototoxicity in children: A consensus review on mechanisms, predisposition, and protection, including a new International Society of Pediatric Oncology Boston ototoxicity scale. J Clin Oncol 30:2408-2417, 2012

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Use of Sodium Thiosulfate as an Otoprotectant in Patients With Cancer Treated With Platinum Compounds: A Review of the Literature

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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APPENDIX

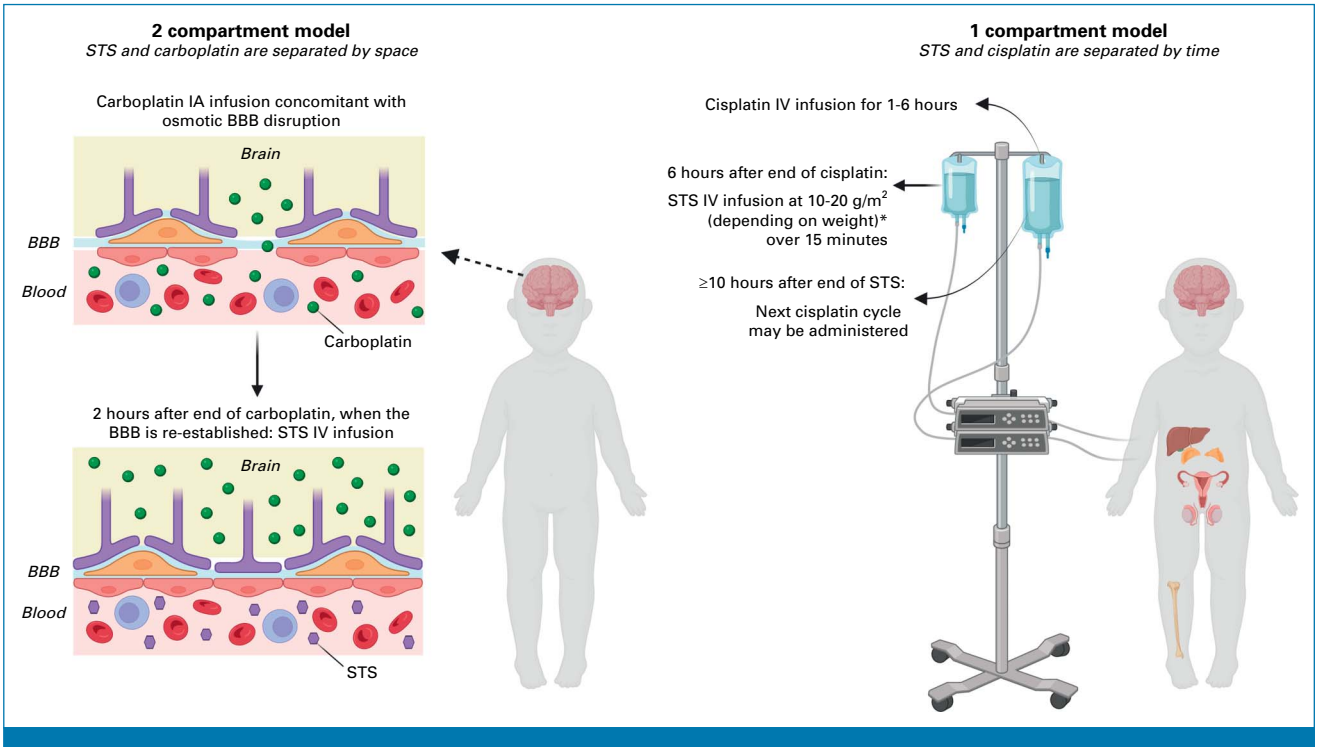

FIG A1. Differences between (A) 2-compartment and (B) 1-compartment models for platinum and STS administration. [a]<5 kg: 10 mg/m^2; 5-10 kg: 15 mg/m^2; >10 kg: 20 mg/m^2. BBB, blood-brain barrier; IA, intra-arterial; IV intravenous; STS, sodium thiosulfate. Created via BioRender.com.