Ototoxicity management and long-term follow-up: acting now for a better future ahead

Norgine Educational Symposium

51st AIEOP National Congress, Lecce, 12-14th October 2026

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The child first and always

UCL

1425

SIOPEL

Childhood Liver Tumours Strategy Group - SIOPEL

SIOPEN NEUROBLASTOMA RESEARCH NETWORK

Faculty Disclosure Dr Brock

Company Name	Honoraria/ Expenses	Consulting/ Advisory Board	Funded Research	Royalties/ Payment	Stock Options	Ownership / Equity Position	Employee	Other (please specify)
Fennec Pharma and Norgine	X	X						

Outline

- The evolving focus on cisplatin induced hearing loss CIHL
- The development of CIHL grading scales and their clinical application
- The clinical burden of CIHL across different tumour types: incidence and risk factors
- The role of STS: mechanism of action, pharmacokinetics, randomized clinical trials
- Implementing STS into clinical practice
- Central review of audiograms & Hearing Related Q of L in all future clinical trials

The evolving focus on CIHL

Symptoms of Cisplatin Toxicity
in Infants and Children

Nausea and vomiting
- Solution: Minimised by the introduction of the HT3 inhibitors

Renal Insufficiency
- Solution: Minimised through adequate hydration with sufficient chloride concentration and mannitol

Peripheral Neurotoxicity
- Dose limiting in adults
- Rarely a problem in children

Hearing Loss
- **Permanent, bilateral, individual genetic susceptibility**

Brock P. et.al. An Increased Loading Dose of Ondansetron: a North European, Double-blind Randomised Study in Children, Comparing 5 mg/m² with 10 mg/m². Eur J Cancer 1996; 32A, 10: 1744-8.
Brock P. et.al. Partial reversibility of cisplatin nephrotoxicity in children. J. Pediatr 1991; 118, 531-4.

Reducing Cisplatin Induced Hearing Loss

Eliminate	Eliminate cisplatin
Reduce	Reduce cisplatin dose
Replace	Replace cisplatin with a less ototoxic platinum agent
Explore	Explore the mechanism of cisplatin ototoxicity and target the pathways: working academically as well as with pharmaceutical companies and regulatory authorities

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cisplatin versus Cisplatin plus Doxorubicin for Standard-Risk Hepatoblastoma

Giorgio Perilongo, Rudolf Maibach, Elisabeth Shafford et al., 2009

Conclusion: Cisplatin monotherapy is not inferior to CisPlatin and Doxorubicin (PLADO) in patients with carefully staged SR HB and eliminates cardiotoxicity

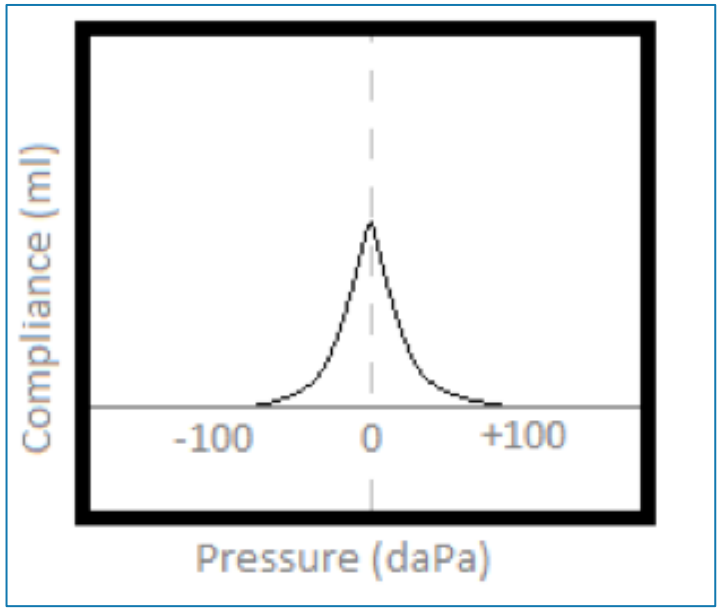
Three-year OS Cis 95% (95% CI, 91-99) and PLADO 93% (95% CI, 88-98)

But: Many children had permanent Brock ≥1 bilateral high-frequency hearing loss

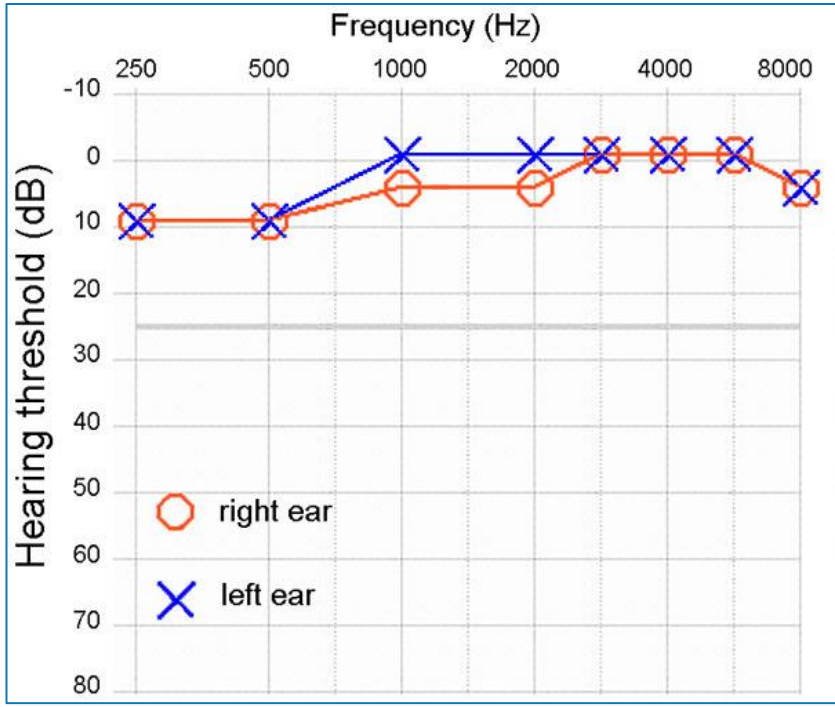
CIHL grading scales

Pure Tone Audiogram
of High Frequency Hearing Loss

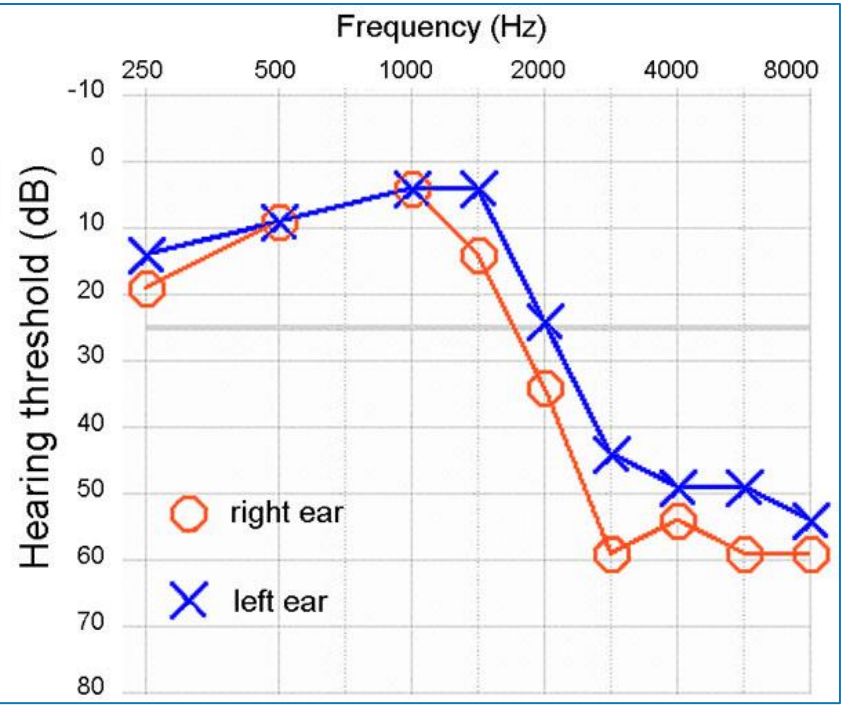
Normal tympanogram



Baseline



End of treatment (6 months)



Child responded reliably

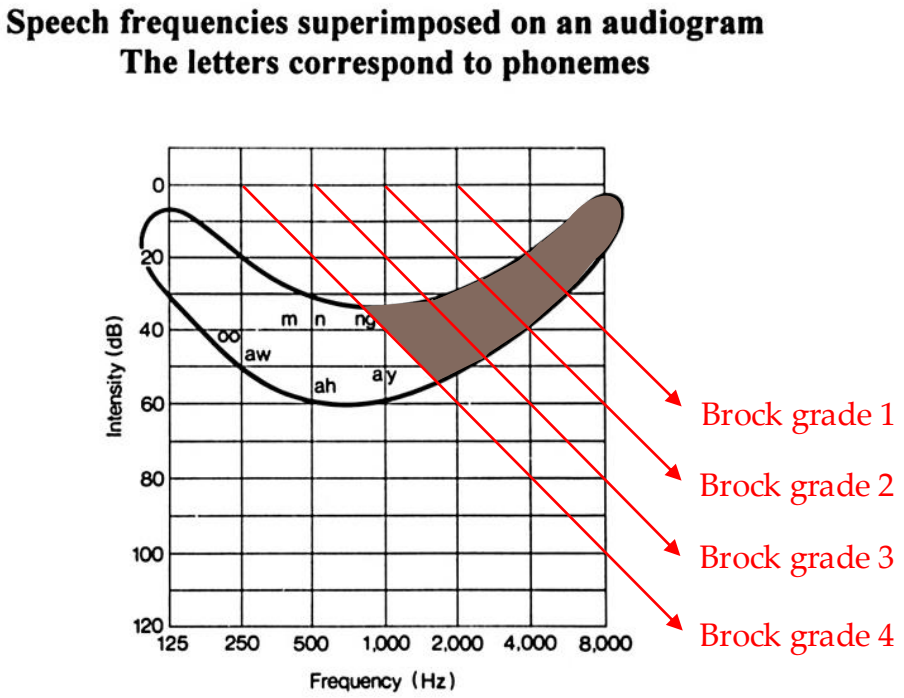
Brock Classification of Cisplatin-Induced Bilateral Hearing Loss

Bilateral Hearing Loss	Grade	Designation
< 40 dB at all frequencies	0	Minimal
≥ 40 dB at 8,000 Hz only O	1	Mild
≥ 40 dB at 4,000 Hz and above O	2	Moderate
≥ 40 dB at 2,000 Hz and above O	3	Marked
≥ 40 dB at 1,000 Hz and above O	4	Severe

The results used are obtained by pure-tone audiometry, from the "better" ear.
Brock grade 0 is not necessarily equivalent to normal hearing.

Taken from Brock PR et al. Cisplatin ototoxicity in children: a practical grading system. Med Pediatr Oncol 1991; 19, 4: 295-300.

Brock Grading and Speech



“The cat sat on the mat” becomes “ e a a on e a”

SIOP Boston Classification of Cisplatin-induced Bilateral Hearing Loss

Bilateral hearing loss	Grade	Designation
≤ 20 dB at all frequencies	0	Normal
≥ 20 dB at 6,000 or 8,000 Hz and above	1	Minimal
≥ 20 dB at 4,000 Hz and above	2	Mild
≥ 20 dB at 2,000 or 3,000 Hz and above	3	Moderate
≥ 40 dB at 2,000 Hz and above*	4	Marked

The results used are obtained by pure-tone audiometry, from the "better" ear

*< 40 dB at all lower frequencies.

Taken from Brock PR 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 2012;30:2408-2417.

CIHL across different tumour types

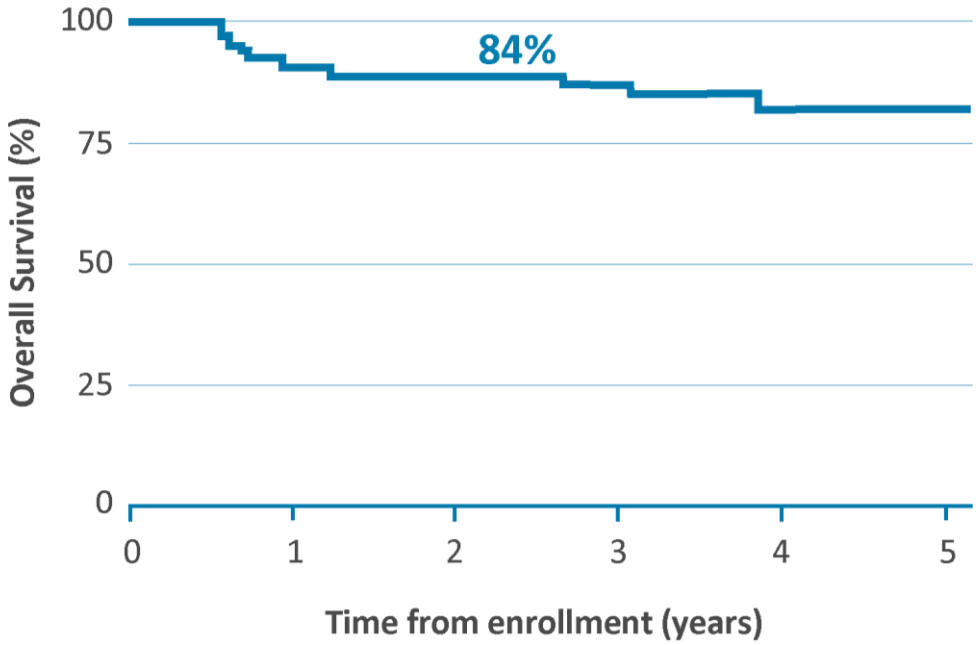
Cisplatin Chemotherapy

Cisplatin is used in the treatment of:

- Brain tumours; medulloblastoma, ependymoma
- Neuroblastoma
- Osteosarcoma
- Liver cancer; hepatoblastoma, HCC
- Germ cell tumours

An estimated 2000 children* are treated with cisplatin in the United States every year[3]

Overall Survival for Patients with Solid Tumours requiring Cisplatin-based Therapy[3]



*Aged 1-15.

References: 1. Gold JM, Raja A. Cisplatin (Cisplatinum) NCBI Bookshelf. Accessed June 10, 2022. https://www.ncbi.nlm.nih.gov/books/NBKt5476 **2.** Varan A, et al. *Pediatr Hematol Oncol.* 2012;29(6):529-537. **3.** Freyer DR, et al. *Lancet Oncology*. 2017;18(1):63-74.

Prevalence and Risk Factors

for Cisplatin-induced Hearing Loss in Children, Adolescents, and Young Adults: a multi-institutional North American cohort study

Inclusion: age 0-39 yrs with a cisplatin treated tumour

Follow up audiology (mean 3-9 yrs): graded by SIOP classification

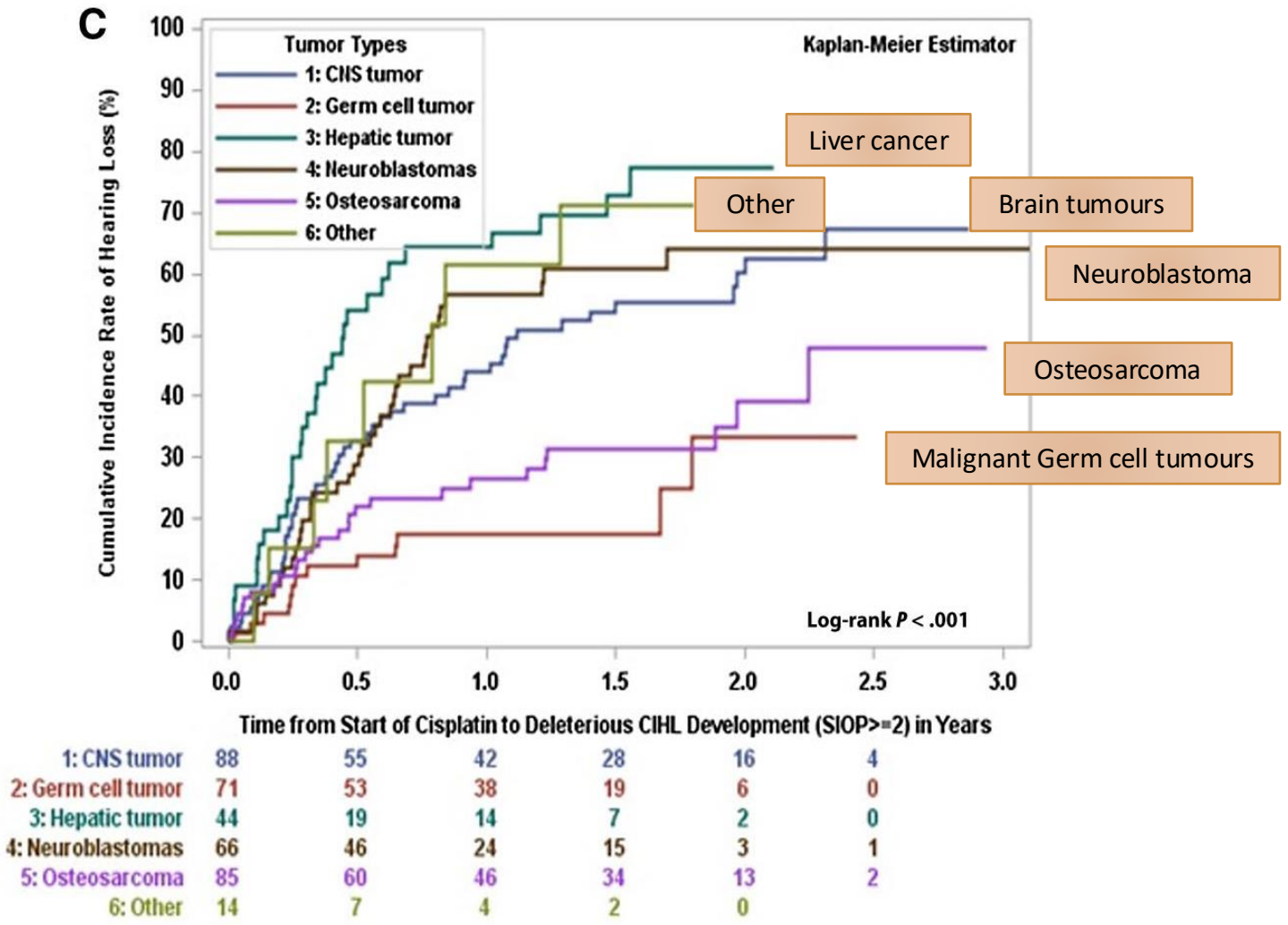
620/1414 (43.8%) developed moderate to severe CIHL

- Age <5 yrs 59.4%
- CNS tumour 50.9%
- Hepatoblastoma 65.9%
- Neuroblastoma 62.1%

Increased risk

- Higher cumulative dose of cisplatin
- Higher fractionated dose of cisplatin per day
- Vincristine exposure

Taken from: Lancet Child Adolesc Health 2021;5:274-83 Diana J Moke et al.

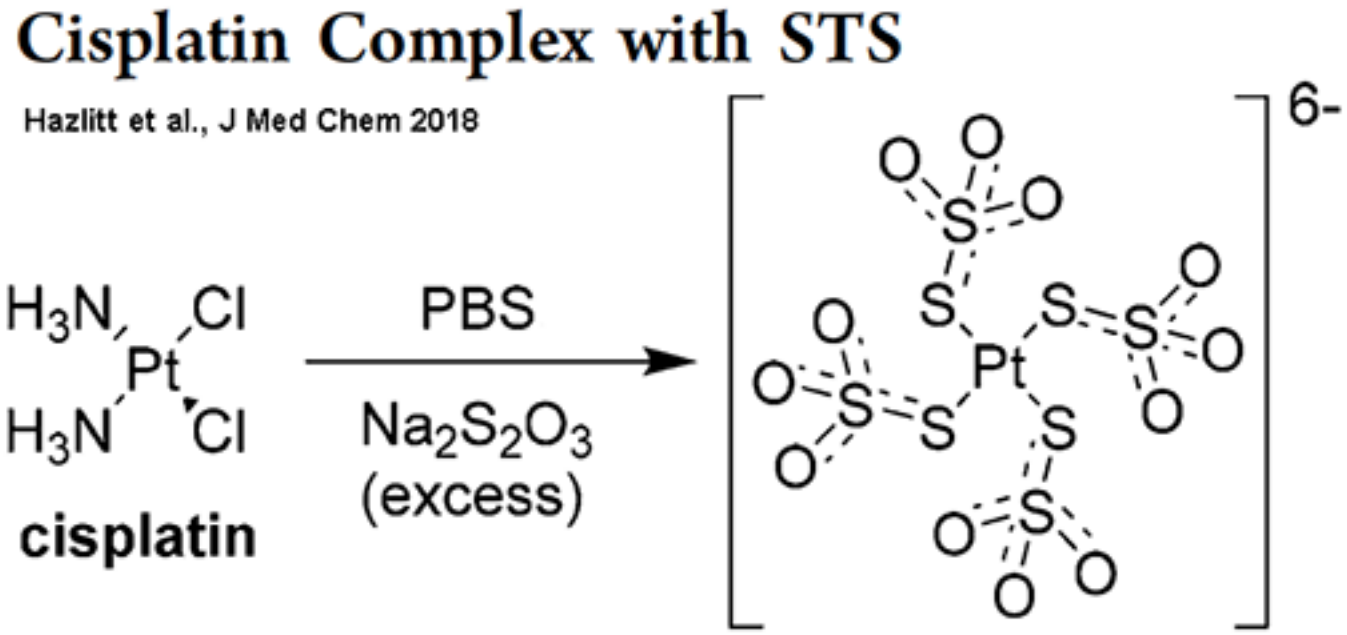


The Cumulative Incidence of Hearing Loss by Tumour Type

Meier AJM 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 2022;128:169-179

Prevention and the role of STS

STS Chemoprotection



Cisplatin is an alkylating agent, a type of chemotherapy which prevents cells from dividing and replicating by damaging their DNA.

Once cisplatin is complexed with STS it is inactivated.

The challenge is not to inactivate the cisplatin before it has done its work on the tumour but to inactivate it at the level of the cochlea in the ear before it destroys the outer hair cells.

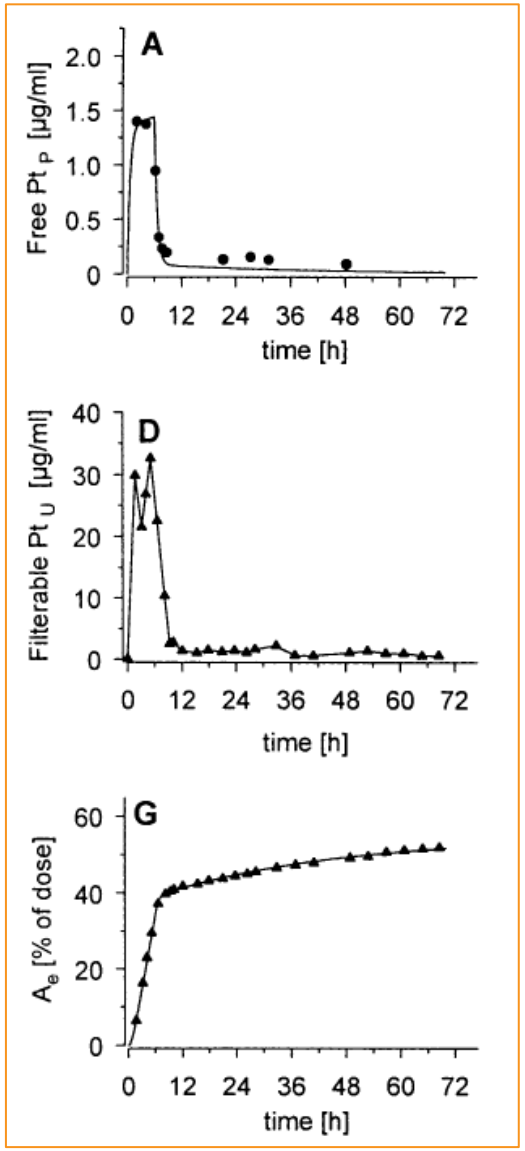
The key is in the timing, harnessing the slower metabolism of the inner ear.

Sodium thiosulfate is not yet commercially available in Italy for ototoxicity prevention. For scientific exchange only.

Pharmacokinetics of Cisplatin Use in Pediatric Patients

Time courses of free platinum concentrations after a single six-hour infusion of 75 mg/m2 of cisplatin.

- in plasma (PtP) A.
- in urine (PTU) D.
- and of cumulative urinary platinum excretion G.



Source: Erdlenbruch B. et al. Eur J Clin Pharmacol 2001;57:393-402.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sodium Thiosulfate for Protection from Cisplatin-Induced Hearing Loss

Penelope Brock, Rudolf Maibach, Margaret Childs et al., 2018

Conclusion: The addition of sodium thiosulfate, administered 6 hours after cisplatin chemotherapy, resulted in a lower incidence of cisplatin-induced hearing loss among children with standard risk hepatoblastoma, without jeopardizing overall or event-free survival.

Sodium thiosulfate is not yet commercially available in Italy for ototoxicity prevention. For scientific exchange only.

Brock PR et al. Sodium thiosulfate for protection from cisplatin-induced hearing loss. N Engl J Med. 2018 Jun 21;378(25):2376-2385.

STS Reduces the Risk of Cisplatin Ototoxicity by approximately 50%

Results for Hearing Loss	SIOPEL 6 ITT Population		COG ACCL0431 ITT Population	
	CIS Alone (N=52)	CIS+STS (N=57)	Observation (N=55)	CIS+STS (N=49)
Yes, n (%)	35 (67.3)	20 (35.1)	31 (56.4)	14 (28.6)
No, n (%)	17 (32.7)	37 (64.9)	24 (43.6)	35 (71.4)
Relative Risk (95% CI)	0.519 (0.356, 0.755)		0.516 (0.318, 0.839)	
P-value	0.0005		0.0040	

Abbreviations: ASHA=American Speech-Language-Hearing Association; CI=confidence interval; CIS=cisplatin; CMH=Cochran-Mantel-Haenszel; OR=odds ratio; RR=relative risk; STS=sodium thiosulfate.

[a] Primary analysis: relative risk and p-value from CMH test stratified by country group, PRETEXT group, and age group.
[b] Primary analysis: based on logistic regression including treatment and stratification variables as covariates in the model.

Sodium thiosulfate is not yet commercially available in Italy for ototoxicity prevention. For scientific exchange only.

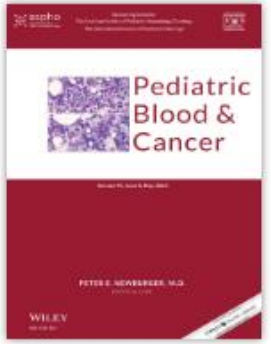
Including STS in clinical practice

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COMMENTARY | Open Access

Sodium thiosulfate as cisplatin otoprotectant in children: The challenge of when to use it

Penelope Brock, Annelot Meijer, Per Kogner, Marc Ansari, Michael Capra, James Geller, Marry van den Heuvel-Eibrink, Kristin Knight, Mariana Kruger, Susan Lindemulder, Rudolf Maibach, Allison O'Neill, Vassilios Papadakis, Kaukab Rajput, Archie Bleyer, Eric Bouffet, Michael Sullivan

First published: 11 February 2023 | https://doi.org/10.1002/pbc.30248

Senior authors Archie Bleyer, Eric Bouffet, and Michael Sullivan contributed equally to this work.

Sodium thiosulfate is not yet commercially available in Italy for ototoxicity prevention. For scientific exchange only.

Prevention of cisplatin-induced hearing loss in children: achievements and challenges for evidence-based implementation of sodium Thiosulfate

Annelot J. M. Meijer[1], Franciscus A. Diepstraten[1*], Marry M. van den Heuvel-Eibrink[1,2*] and Archie Bleyer[3]

[1]Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands, [2]Wilhelmina Childrens Hospital, University of Utrecht, Utrecht, Netherlands, [3]Radiation Oncology, Knight Cancer Institute, Oregon Health and Science University, Portland, OR, United States

Ototoxicity is a devastating direct, irreversible side effect of platinum use in children with cancer, with its consequent effect on speech, language and social development, quality of life and adult productivity. Cisplatin, an essential chemotherapeutic agent for the treatment of solid tumors in children, is a DNA cross-linking agent. Which causes hearing loss in 50-70% of cisplatin treated children. Fortunately, to prevent hearing loss, sodium thiosulfate (STS), which binds to cisplatin, and reduces the superoxides in both tumor and outer hair cells of the cochlea has now been discovered to be an effective and safe otoprotectant if administered correctly. The aim of this perspective paper is to explore the key safety issues and challenges important for pediatric oncologists and pharmacists when considering the clinical use of STS as an otoprotectant for children and adolescents receiving cisplatin. These include: the choice of the formulation; the timing, both that of the STS in relation to cisplatin as well as the timing of the cisplatin infusion itself; the dosing; the challenge left by the definition of localized versus disseminated disease and the difference in indication for STS, between cisplatin treated patients and those receiving another platinum chemotherapeutic agent, carboplatin.

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

Annelot J.M. Meijer, PhD[1]; Franciscus A. Diepstraten, MD[1]; Marc Ansari, MD, PhD[2]; Eric Bouffet, MD, PhD[3]; Archie Bleyer, MD, PhD[4]; Brice Fresneau, MD, PhD[5]; James I. Geller, MD, PhD[6]; Alwin D.R. Huitema, PhD[1,7,8]; Per Kogner, MD, PhD[9]; Rudolf Maibach, MD, PhD[10]; Allison F. O'Neill, MD, PhD[11]; Vassilios Papadakis, MD, PhD[12]; Kaukab M. Rajput, MD, FRCP[13]; Gareth J. Veal, PhD[14]; Michael Sullivan, MD, PhD, FRACP[15]; Marry M. van den Heuvel-Eibrink, MD, PhD[1,16]; and Penelope R. Brock, MD, PhD[17]

DOI https://doi.org/10.1200/JCO.23.02353

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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J Clin Oncol 00:1-14
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View Online Article

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Sodium thiosulfate is not yet commercially available in Italy for ototoxicity prevention. For scientific exchange only.

AJM Meijer et al. Prevention of cisplatin-induced hearing loss in children: Achievements and challenges for evidence-based implementation of sodium thiosulfate. Frontiers in Oncology, Perspective paper, 18 March 2024, DOI 10.3389/fonc2024.1336714

AJM Meijer et al. Use of sodium thiosulfate as an otoprotectant in patients with cancer treated with platinum compounds: A review of the literature. J Clin Oncol, Narrative Review, 22 April 2024, DOI 10.1200/JCO.23.02353

Future clinical trials including cisplatin

CIHL Grading applied to all children

- All future clinical trials, where cisplatin is part of the treatment, should be designed to include the uploading of audiograms onto the clinical trial database

- They can then be centrally reviewed and any grading scale applied

Hearing Related Quality of Life

- Health Related Quality of Life will not adequately show the impact of CIHL on children's lives
- Specific Hearing Related Quality of Life is required
- Age appropriate Hearing Related Quality of Life scales
  - urgently need to be validated in all European languages
  - then applied to future clinical trials

M. Migotsky et al. Impact of Cisplatin-Induced Hearing Loss on Quality of Life in Childhood Cancer Survivors. JCO Oncol Pract June 22, 2026 DOI https://doi.org/10.1200/OP-25-01414
K. Rajput et al. Ototoxicity-induced hearing loss and quality of life in survivors of paediatric cancer. Int J Pediatr Otorhinolaryngol 2020 Nov: 138: 110401 doi: 10.1016/j.ijporl.2020.110401.





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To Jon Pritchard and Jack Plaschkes for inspiration.

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To David Freyer and Lillian Sung.

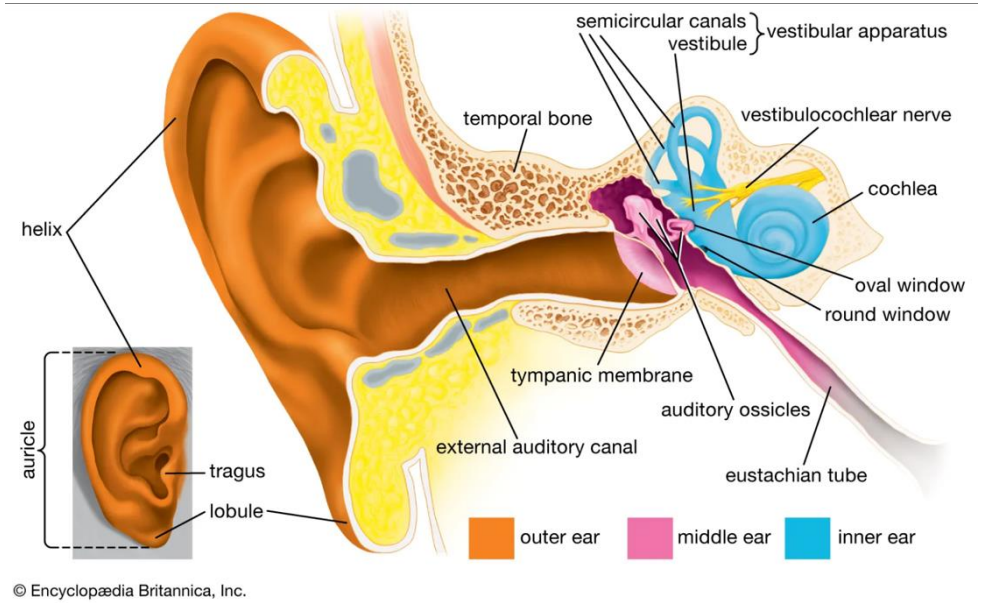
To all my SIOPEL colleagues.

To Fennec Pharma for providing STS.

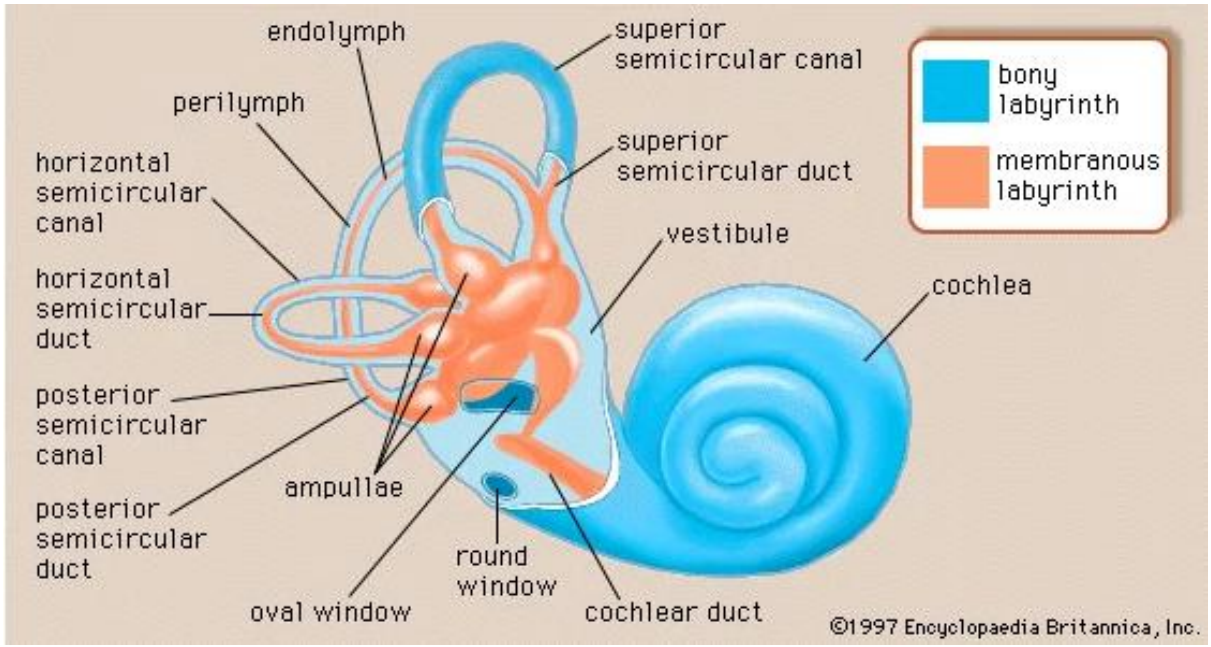
To CINECA for the SIOPEL database.

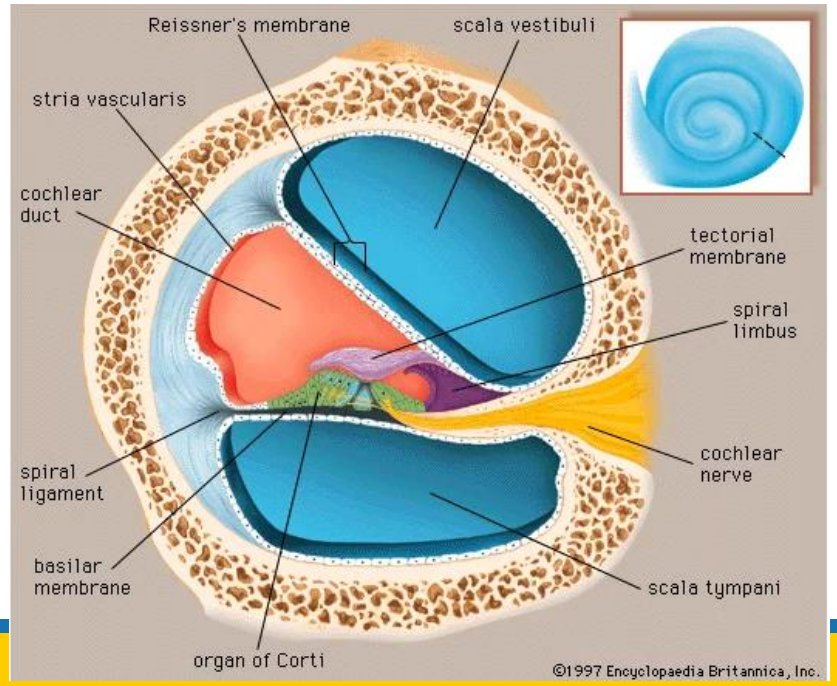
To National charities for funding.

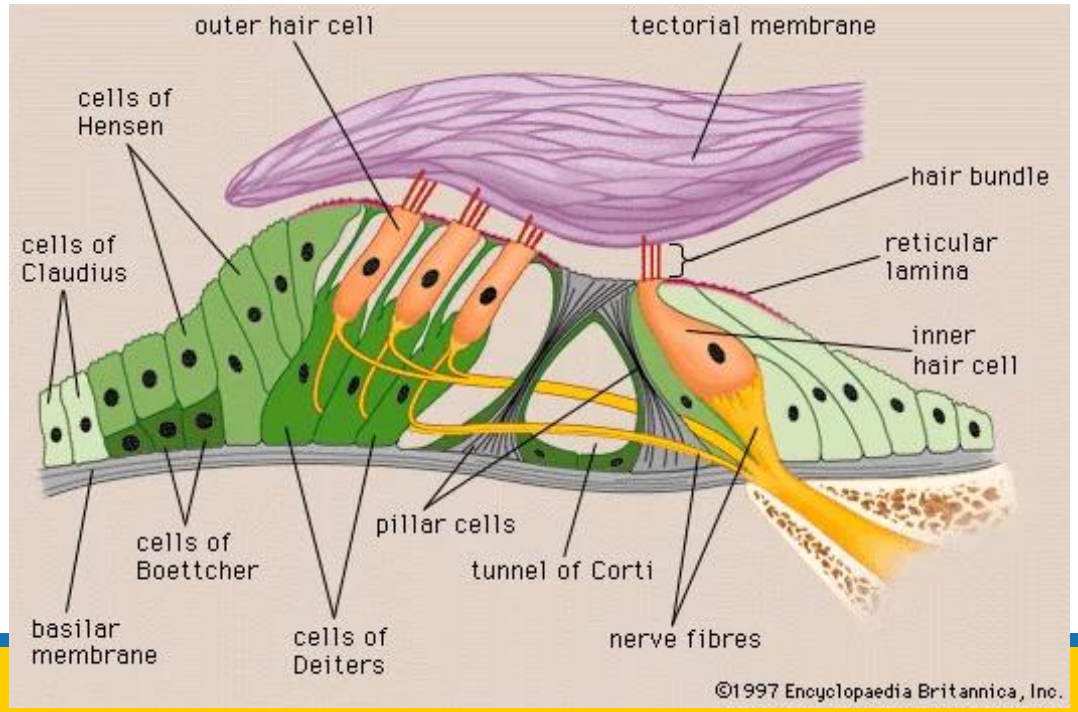
Backup slides



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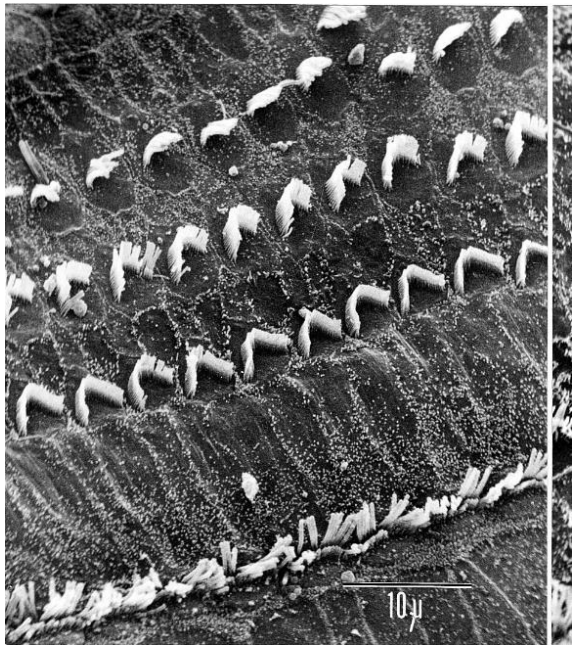


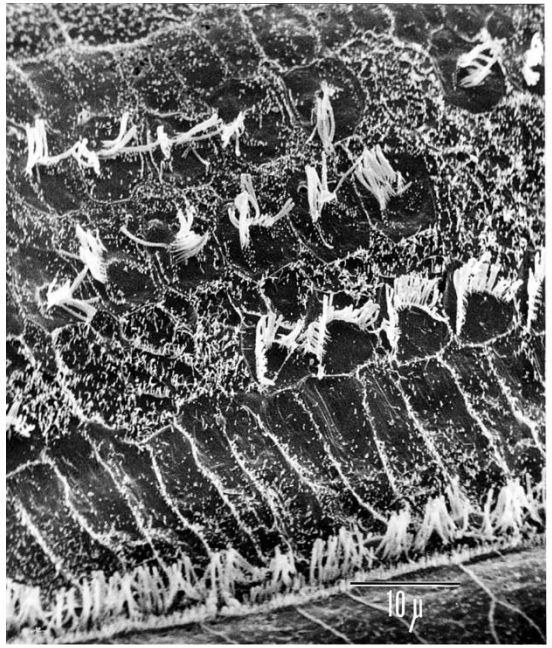


Damage to the Hair Cells

Organ of Corti | Healthy (from guinea pig)

- Portion of a healthy organ of Corti from a guinea pig showing the characteristic three rows of outer hair cells and single row of inner hair cells.





The same damage occurs when you treat a child with cisplatin chemotherapy

Organ of Corti | Damaged (from guinea pig)

- Portion of a noise-damaged organ of Corti from a guinea pig exposed to sound at a 120-decibel level, similar to that experienced at a heavy metal rock concert, showing "scars" that have replaced many of the outer hair cells and showing the remaining stereocilia in disarray.
- Hearing is permanently damaged because lost hair cells will not be replaced, and injured cells may be dying.

https://www.britannica.com/science/ear#/media/1/175622/530

STS Mechanism of Action

Mechanism of Cisplatin-induced Ototoxicity

- Anticancer activity of cisplatin occurs during the first two hours after administration when the free (unbound) cisplatin distributes into the cancer cells
- Cisplatin (CIS) is readily cleared from most organs but is retained longer term in the cochlea
- Cisplatin-induced ototoxicity is caused by irreversible damage to hair cells in the cochlea
- The cochlea is very sensitive to oxidative stress, which has been shown to be involved in ototoxicity
- The cochlea is very sensitive to oxidative stress, which has been shown to be involved in CIS induced hearing loss.

Intended Mechanism of Action

- The mechanism of STS protection against ototoxicity is not fully understood, but may include increasing levels of endogenous antioxidants, scavenging reactive oxygen species, and direct interaction between CIS and the thiol group in STS.
- **Mainly STS inhibits oxidative stress**
- **Administering STS 6 hours after completion of cisplatin infusion ensures that levels of unbound cisplatin at that time are minimal**
- STS has the ability to enter cells at least partly through the sodium sulfate cotransporter 2 and can cause intracellular effects such as the increase in antioxidant glutathione levels and inhibition of intracellular oxidative stress .

*www.accessdata.fda.gov/scrips/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=184.1807

1. PLATINOL. Cisplatin FDA.gov.pdf; Accessed February 17, 2020. 2. Breglio AM et al. Nature Communications. 2017;8:1654-1663 3. Landier W. Cancer. 2016;122:1647-1658. 4. Langer T et al. Trends in Pharmacological Sciences. 2013;34:458-469 5. Data on file, Fennec Pharmaceuticals 2020. Adopted from Fennec Pharma Corporate and Investor presentations
6.Patent File: https://patentimages.storage.googleapis.com/b4/84/12/8fdf6a517b89c5/US20200009255A1.pdf

Sodium ThioSulfate Injection (STS) Pharmacokinetics

Elimination: The mean half-life (t1/2) of thiosulfate is approximately 20 minutes to 50 minutes. The mean total clearance of thiosulfate is 2.2 mL/min/kg in patients with fully developed renal function (age approximately 1 year). Renal clearance accounts for approximately 50% of total clearance in patients with fully developed renal function.

Metabolism: Thiosulfate is an endogenous intermediate product of sulfur-containing amino acid metabolism. Thiosulfate is metabolized through thiosulfate sulfur transferase and thiosulfate reductase to sulfite, which is oxidized to sulfate.

Excretion: After administration of sodium thiosulfate, approximately 50% of the administered sodium thiosulfate was excreted unchanged in urine and >95% of the dose excreted in urine occurs within the first 4 hours after administration.