Multidisciplinary approach to the management of ototoxicity: collaboration between pediatric oncologist and audiologist/ENT

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University of Bari
Italy

Faculty Disclosure Prof Quaranta

- Sanofi
- Amplifon
- Luxottica
- Amgen
- Norgine

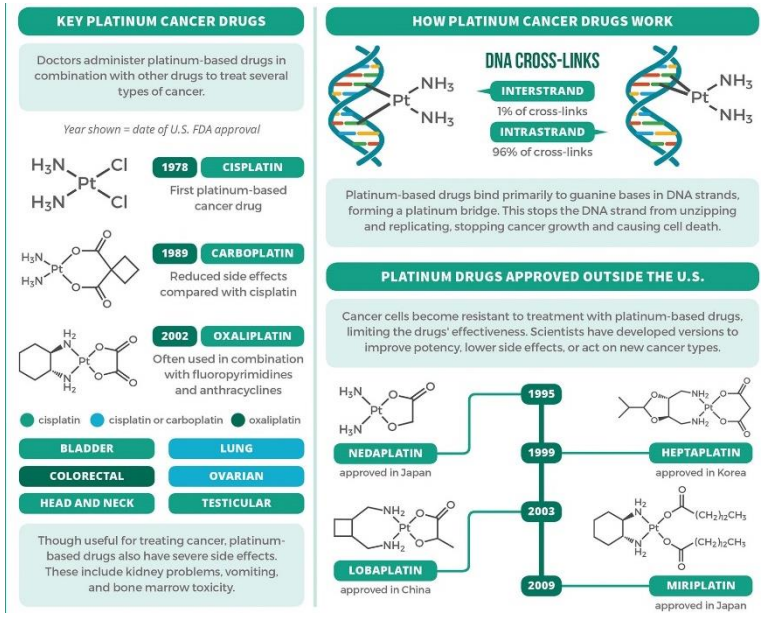


Cisplatin dosages for different types of cancer.

Type of cancer	Cisplatin Dosage
Metastatic testicular cancer	20 mg/m^2 once a day for five days per cycle
Metastatic ovarian Cancer	(1) 75–100 mg/m^2 on day 1, every 4 weeks (taken with cyclophosphamide 600 mg/m^2 day 1, every 4 weeks) (2) 100 mg/m^2 per cycle once every 4 weeks (As single agent)
Advanced bladder cancer	70 mg/m^2 on day 2, every 4 weeks (with gemcitabine)
Head and Neck cancer	75–100 mg/m^2 on day 1, every 3–4 weeks
Oesophageal cancer	75–100 mg/m^2 on day 1, every 3–4 weeks (with fluorouracil)
Gastric cancer	60 mg/m^2 on day 1, every 3 weeks, (with epirubicin, capecitabine)
Lung cancer	(1) 75–100 mg/m^2 on day 1, every 3–4 weeks (with vinorelbine (2) 50 mg/m^2 on days 1 and 8, every 4 weeks (with etoposide, radiation therapy)
Hodgkin's or non-Hodgkin's lymphoma	75 mg/m^2 on day 1, every 3 weeks (with dexamethasone, gemcitabine)
Osteosarcoma	100 mg/m^2 on day 1, every 3 weeks (with doxorubicin)

First choice drug in pediatric cancers (compared to 26-90% in adults)

Ototoxicy reported in 20-90% of cases in high frequencies.



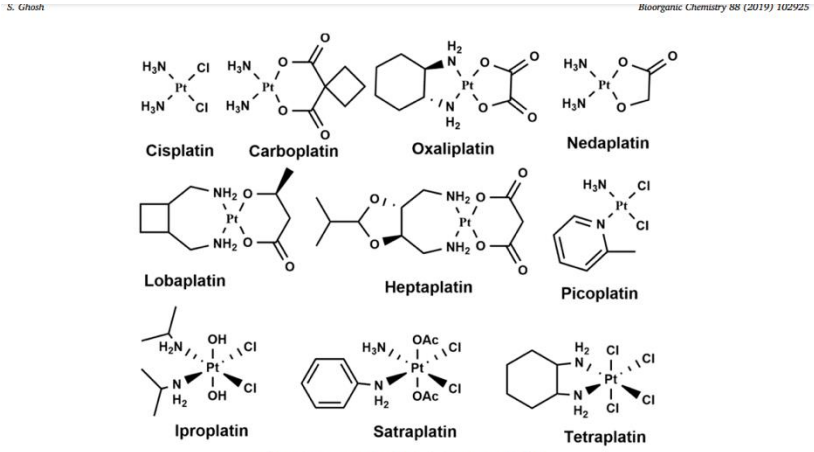
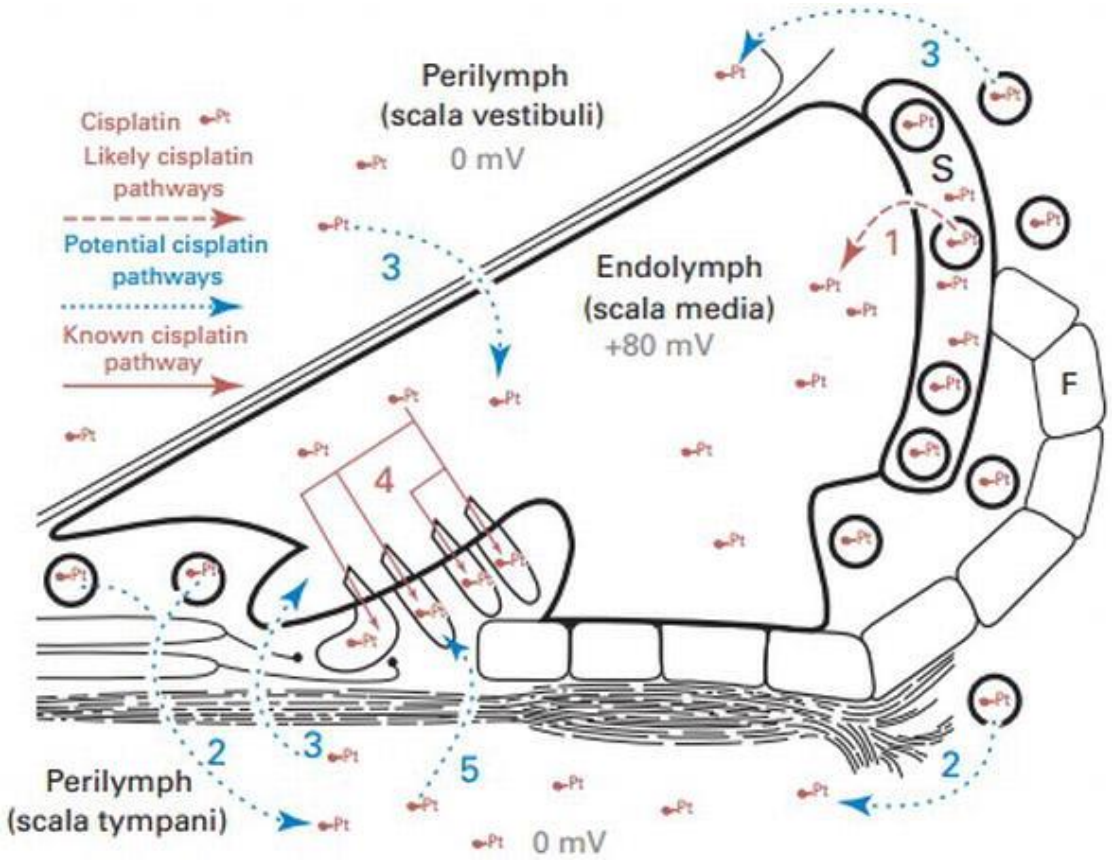


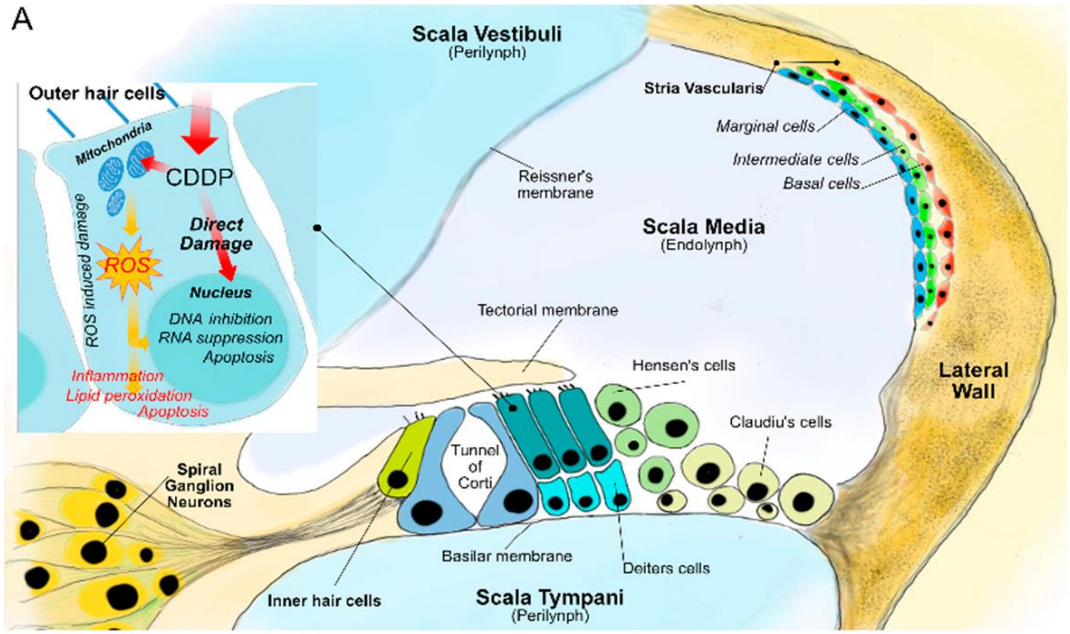
Fig. 6. Some approved and trial platinum anticancer drugs.

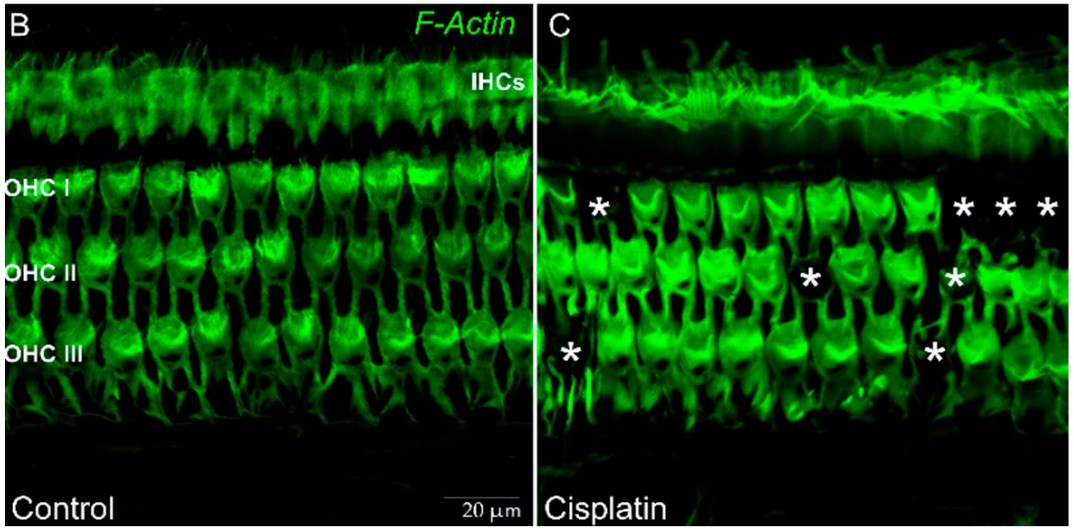
Table 3
Clinically approved Pt(II)-anticancer drugs.

Drug	Year of approval	Country approved	Type of cancer treated
Cisplatin	1978	Worldwide	Testicular, Ovarian, Bladder, Melanoma, NSCLC, Lymphomas, Myelomas cancer
Carboplatin	1989	Worldwide	Ovarian, Retinoblastomas, Neuroblastomas, Nephroblastomas Brain tumor, Head and neck, Cervix, Testis, Breast, Lung, Bladder cancer
Nedaplatin	1995	Japan	NSCLC, SCLC, Oesophageal cancer, Head and neck cancers
Oxaliplatin	1996	Worldwide	Colon cancer
Heptaplatin	1999	Korea	Advanced gastric cancer
Lobaplatin	2010	China	CML, SCLC, Inoperable metastatic breast cancer

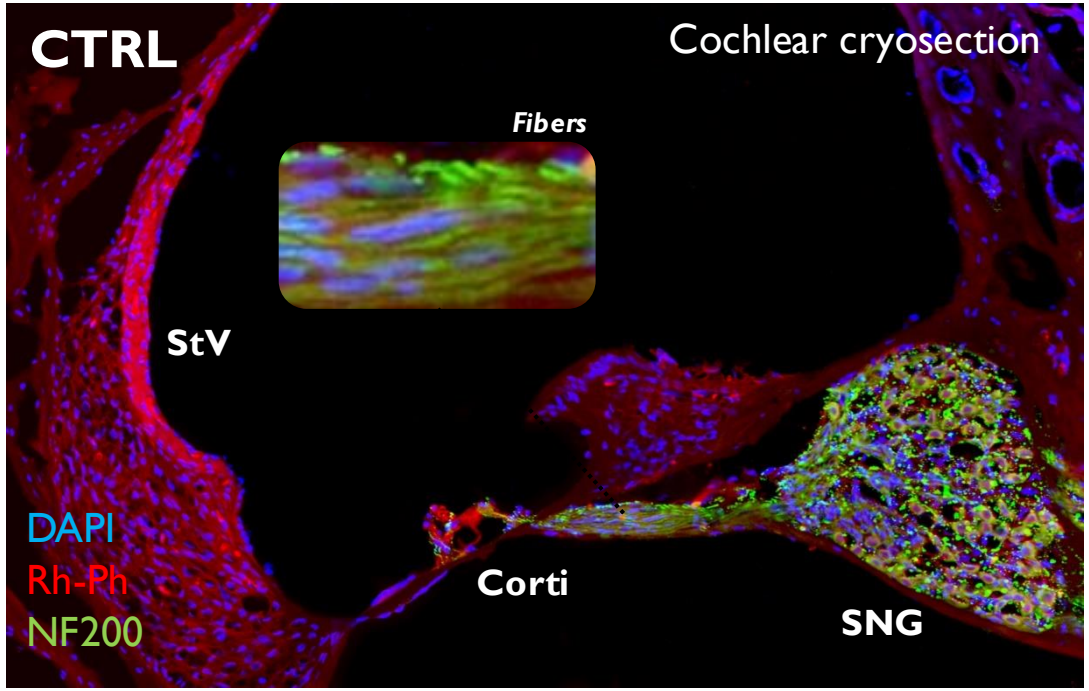
OTOTOXICITY

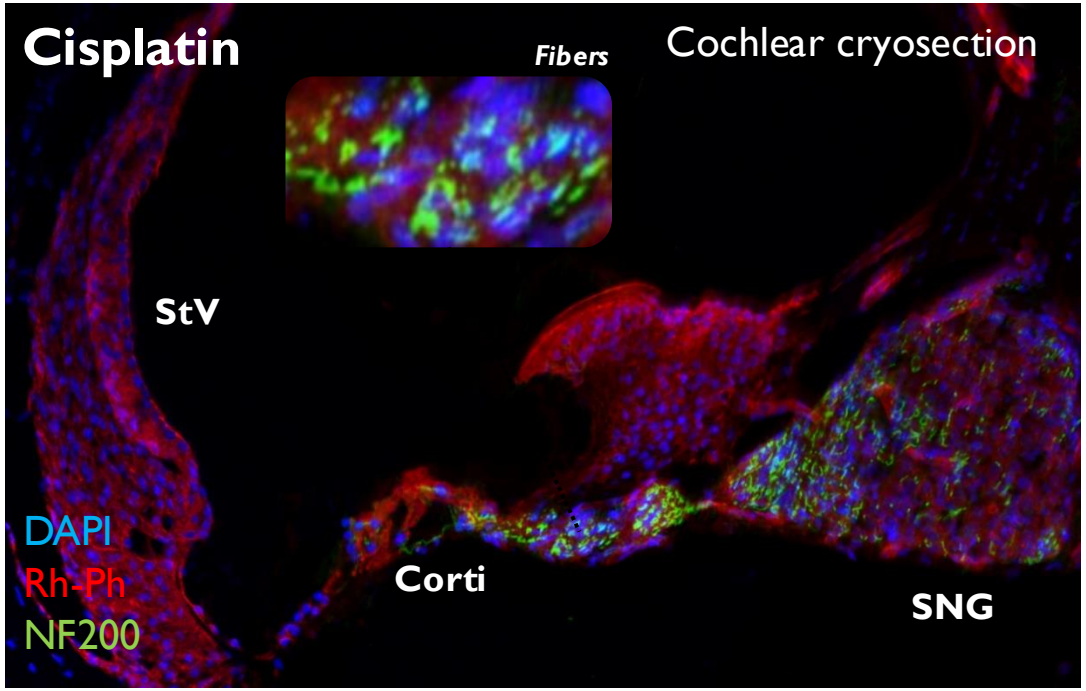


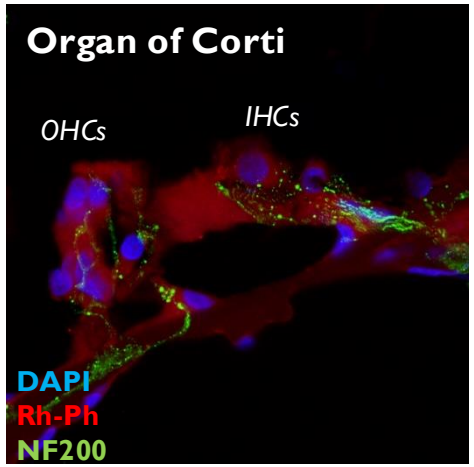


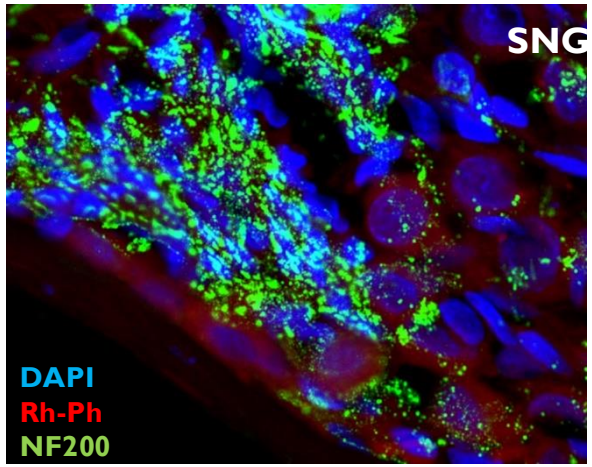


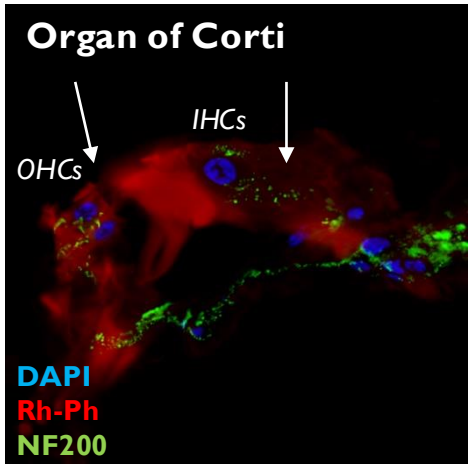
(Romano et al., 2020)

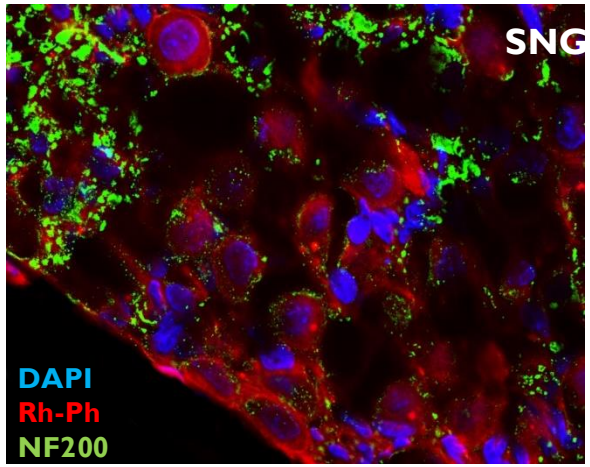

CTRL
Cochlear cryosection
Fibers
StV
Corti
SNG
DAPI
Rh-Ph
NF200


Cisplatin
Fibers
Cochlear cryosection
StV
Corti
SNG
DAPI
Rh-Ph
NF200


Organ of Corti
OHCs
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Rh-Ph
NF200


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Organ of Corti
OHCs
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Available online at www.sciencedirect.com
SCIENCE DIRECT
Hearing Research 182 (2003) 56–64
HEARING RESEARCH
www.elsevier.com/locate/heares

Cisplatin ototoxicity in the guinea pig: vestibular and cochlear damage[1]

Bruno Sergi [a], Aldo Ferraresi [b], Diana Troiani [b], Gaetano Paludetti [a], Anna Rita Fetoni [a,*]

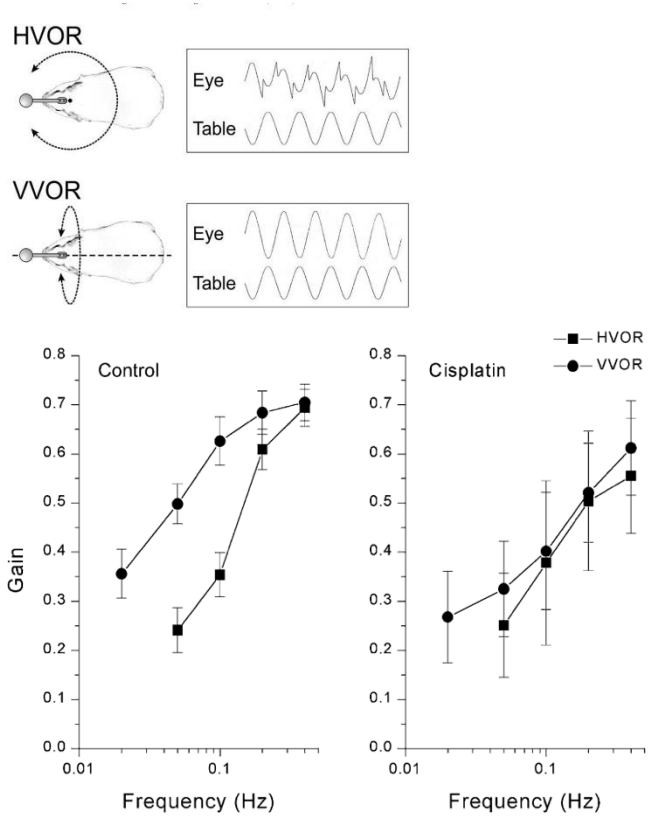
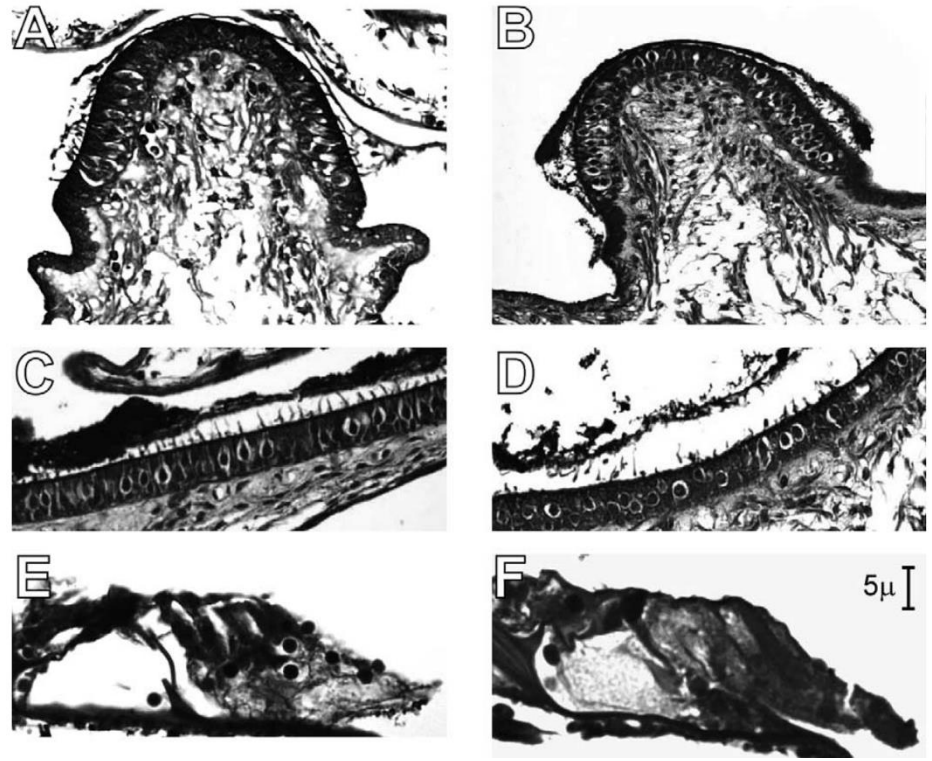
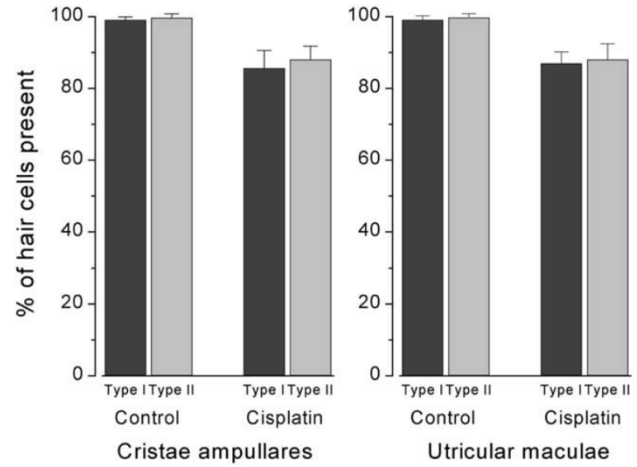


Fig. 3. Comparison of VOR gains (means ± S.D.) obtained in animals after 6 days of treatment with cisplatin ($n = 6$) and in controls ($n = 4$). A 20% reduction of HVOR gain was observed at high frequencies (0.2–0.4 Hz), whereas VVOR gain decreased about 20%, 35% and 25% at high, middle and low frequencies respectively.





Cochrane Library
Cochrane Database of Systematic Reviews

Platinum-induced hearing loss after treatment for childhood cancer (Review)

van As JW, van den Berg H, van Dalen EC

Cochrane Database of Systematic Reviews 2016, Issue 8. Art. No.: CD010181.
DOI: 10.1002/14651858.CD010181.pub2.

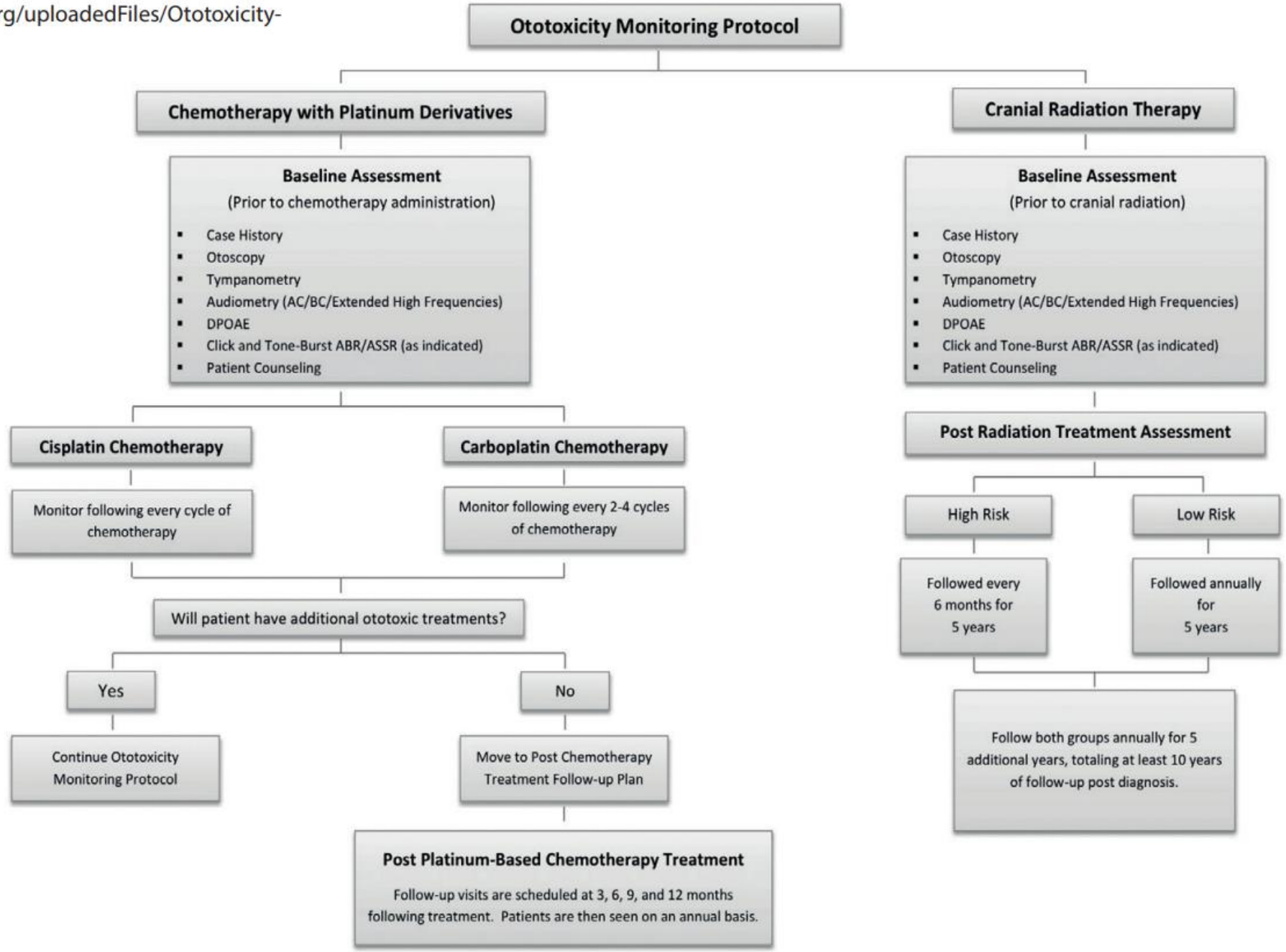
Variable prevalence of ototoxicity from 0% to 90%
Heterogeneity of results and association of risk factors !!!

- Type of chemotherapy used
- Cumulative dose
- Radiation therapy
- Age
- Renal function
- Use of other ototoxic drugs
- Duration of follow-up



Platinum-based therapy, including cisplatin, carboplatin, oxaliplatin or a combination of these, is used to treat a variety of paediatric malignancies. Unfortunately, one of the most important adverse effects is the occurrence of hearing loss or ototoxicity. There is a wide variation in the reported prevalence of platinum-induced ototoxicity and the associated risk factors. More insight into the prevalence of and risk factors for platinum-induced hearing loss is essential in order to develop less ototoxic treatment protocols for the future treatment of children with cancer and to develop adequate follow-up protocols for childhood cancer survivors treated with platinum-based therapy.

The ASHA Flowchart of ototoxicity monitoring protocol for patients with cancer. (www.asha.org/uploadedFiles/Ototoxicity-Monitoring-Protocol-Flowchart.pdf)



Audiological evaluation in the child

- Audiometry (depends on age)
- Tympanometry
- ABR
- OAES



Audiology & Neurotology

Original Paper

Audiol Neurotol 2016;21:203–211
DOI: 10.1159/000442435

Received: March 30, 2015
Accepted: September 24, 2015
Published online: June 11, 2016

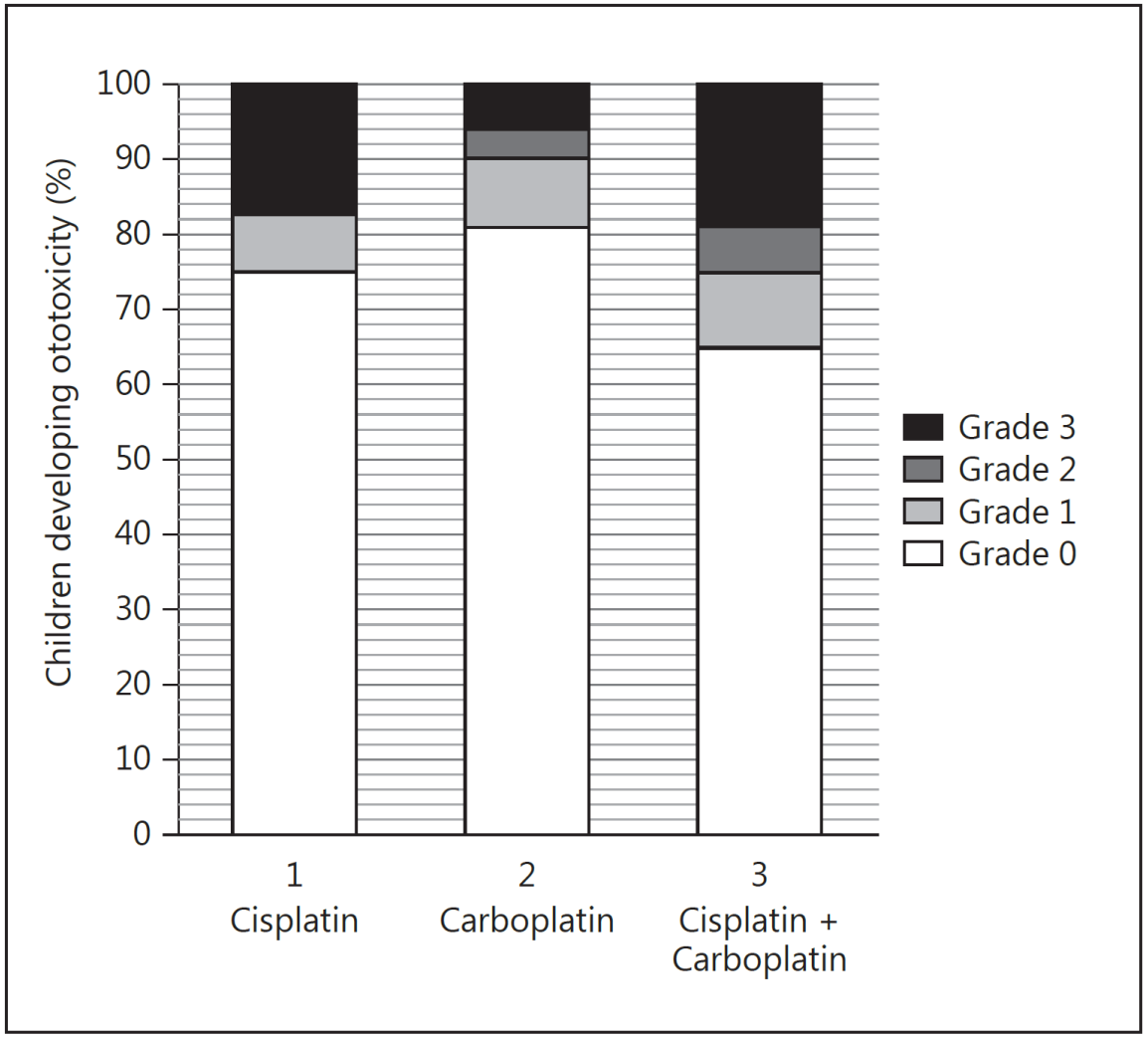
Audiological Monitoring in Children Treated with Platinum Chemotherapy

A.R. Fetoni[a] A. Ruggiero[b] D. Lucidi[a] E. De Corso[a] B. Sergi[a] G. Conti[a]
G. Paludetti[a]

Table 2. SIOP Boston Ototoxicity Scale

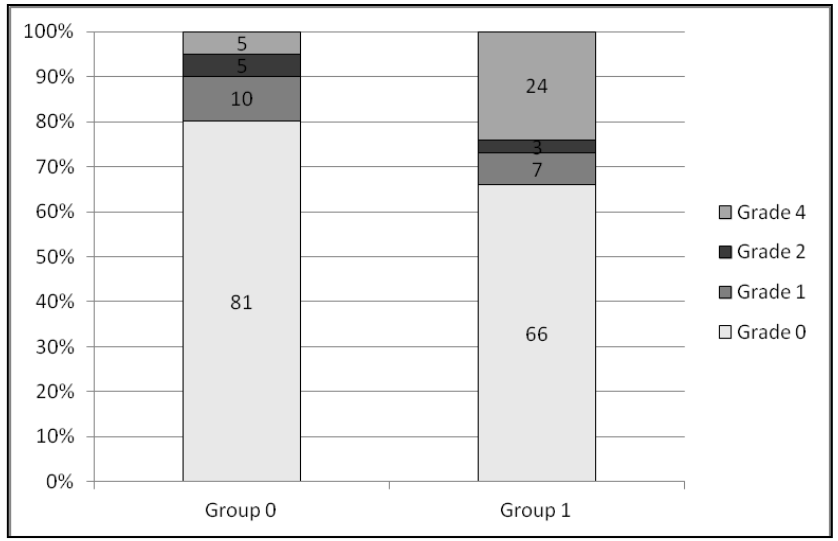
Grade	Parameters
0	≤ 20 dB HL at all frequencies
1	> 20 dB HL (ie, 25 dB HL or greater) SNHL above 4,000 Hz (ie, 6 or 8 kHz)
2	> 20 dB HL SNHL at 4,000 Hz and above
3	> 20 dB HL SNHL at 2,000 Hz or 3,000 Hz and above
4	> 40 dB HL (ie, 45 dB HL or more) SNHL at 2,000 Hz and above

Overall distribution



The effect of radiotherapy

Radiotherapy has a statistically significant influence on the onset and degree of ototoxicity ($p<0.05$)



Moeller et al. Radiation Oncology 2011, 6:58
http://www.ro-journal.com/content/6/1/58

RADIATION ONCOLOGY

RESEARCH Open Access

Low early ototoxicity rates for pediatric medulloblastoma patients treated with proton radiotherapy

Benjamin J Moeller[1], Murali Chintagumpala[2], Jimmy J Philip[1], David R Grosshans[1], Mary F McAleer[1], Shiao Y Woo[3], Paul W Gidley[4], Tribhawan S Vats[5] and Anita Mahajan[1*]

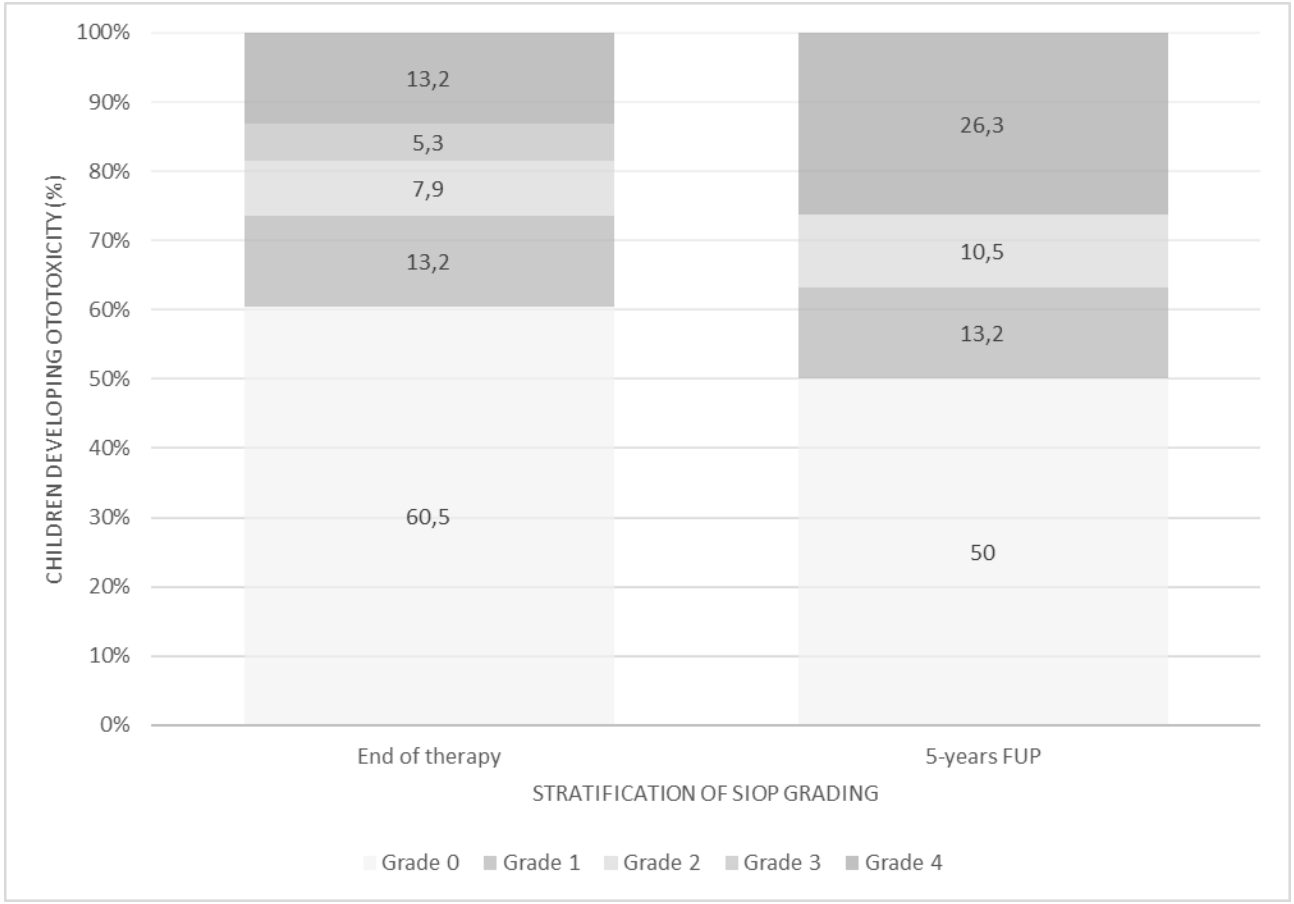
The Ochsner Journal 12:191–196, 2012
© Academic Division of Ochsner Clinic Foundation

Cisplatin and Cranial Irradiation-Related Hearing Loss in Children

Rajasekharan Warrier, MD,* Aman Chauhan, MD,† Murali Davluri, MD,‡ Sonya L. Tedesco, MCDC, CCC-A,§ Joseph Nadell, MD,|| Randall Craver, MD¶

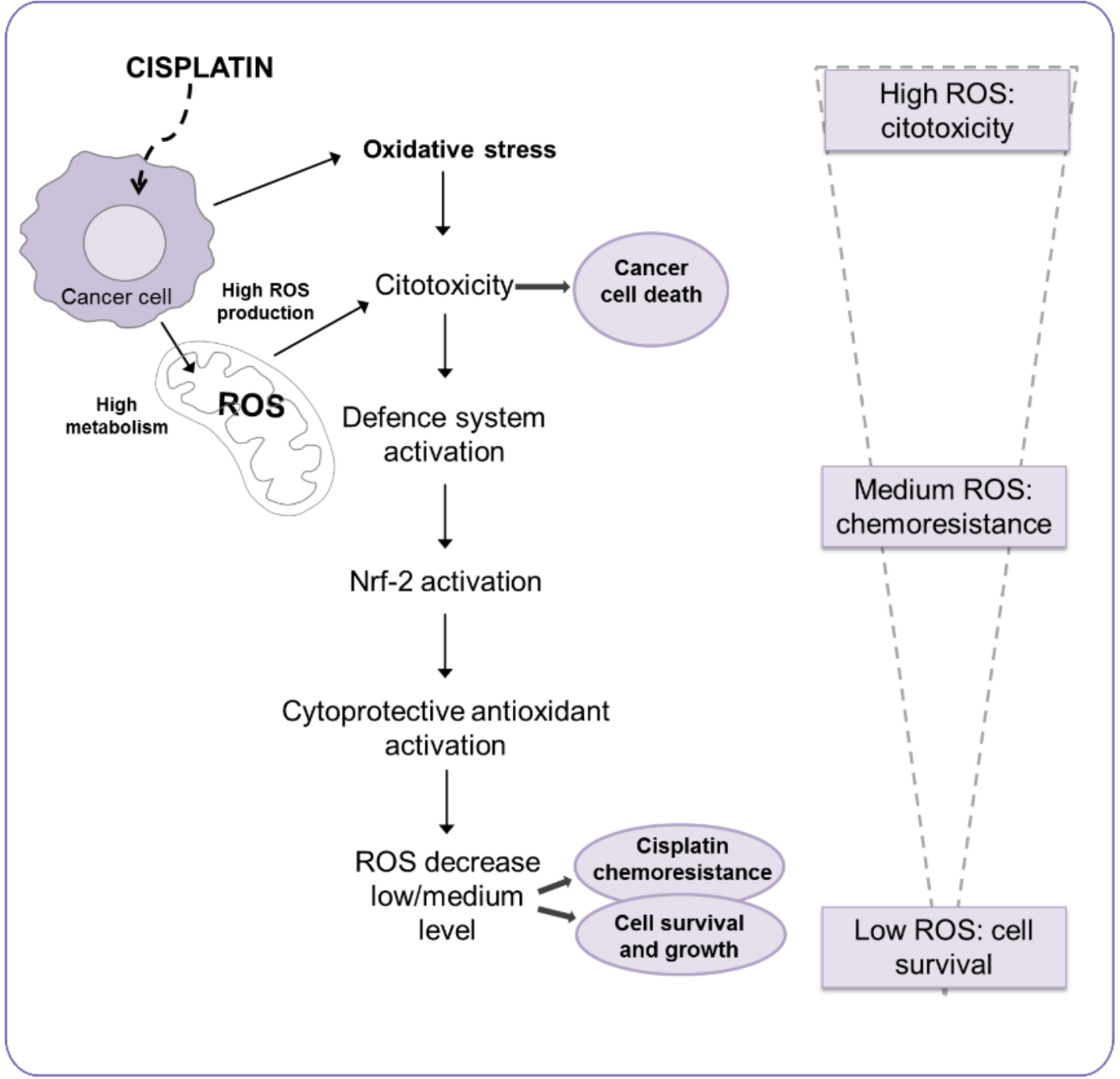
Late ototoxicity

- The percentage of children with ototoxicity at the long-term follow-up was significantly increased compared to that at the end of chemotherapy 52.5% versus 39.5% ($p < 0.001$).
- *26.3% exhibited a progressive hearing loss during the long-term follow-up, and we observed 13% new cases with late onset hearing loss*.
- No patient showed hearing improvement during the hearing monitoring.
- 13% of patients needed hearing aids at the end of long-term follow-up.
- Median time of the late onset/progression of ototoxicity was 24 months by the end of treatment (range: 3–84 months).



Is it possible to prevent ototoxicity?

The level of antineoplastic cytotoxicity as well as ototoxic damage depend on the level of ROS production



Fetoni et al., ARS 2021

SCIENTIFIC REPORTS
nature research

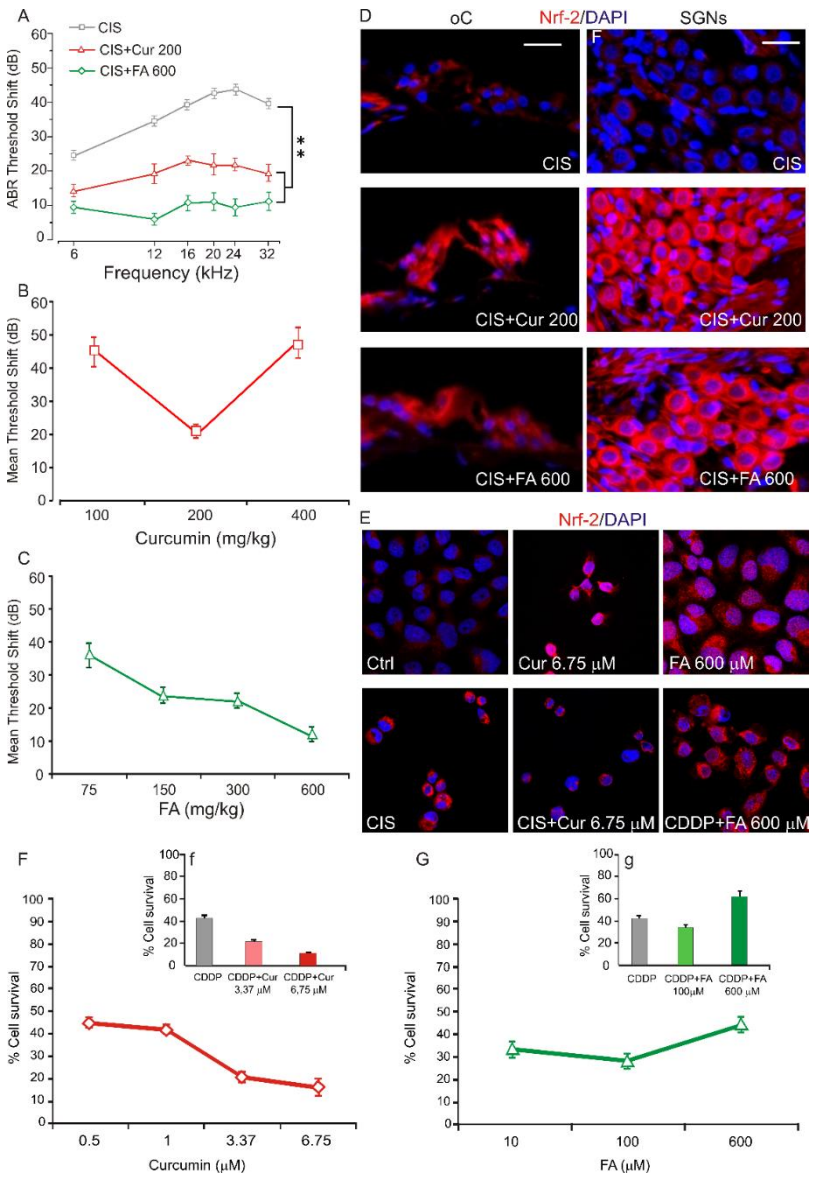
OPEN

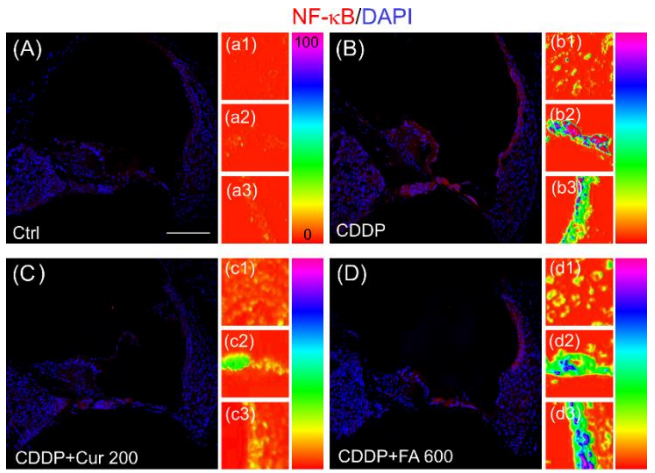
The dual role of curcumin and ferulic acid in counteracting chemoresistance and cisplatin-induced ototoxicity

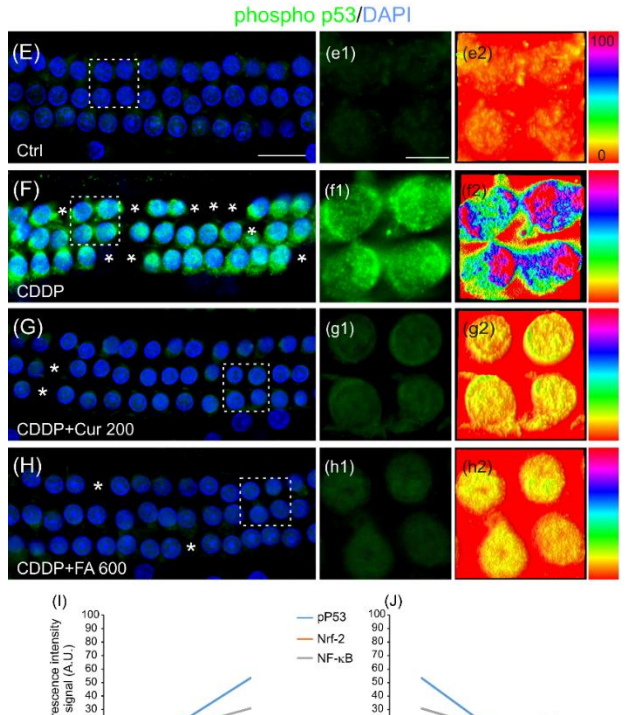
Fabiola Paciello[1,2], Anna Rita Fetoni[2,3*], Daniele Mezzogori[1], Rolando Rolesi[2], Antonella Di Pino[3], Gaetano Paludetti[2,3,4], Claudio Grassi[1,2,4] & Diana Troiani[1,4]

In the cochlea both Curcumin and ferulic acid potentiate the endogenous antioxidant response against cisplatin ototoxicity

Increase the nuclear traslocation of Nrf2 enhancing anti-oxidants effects



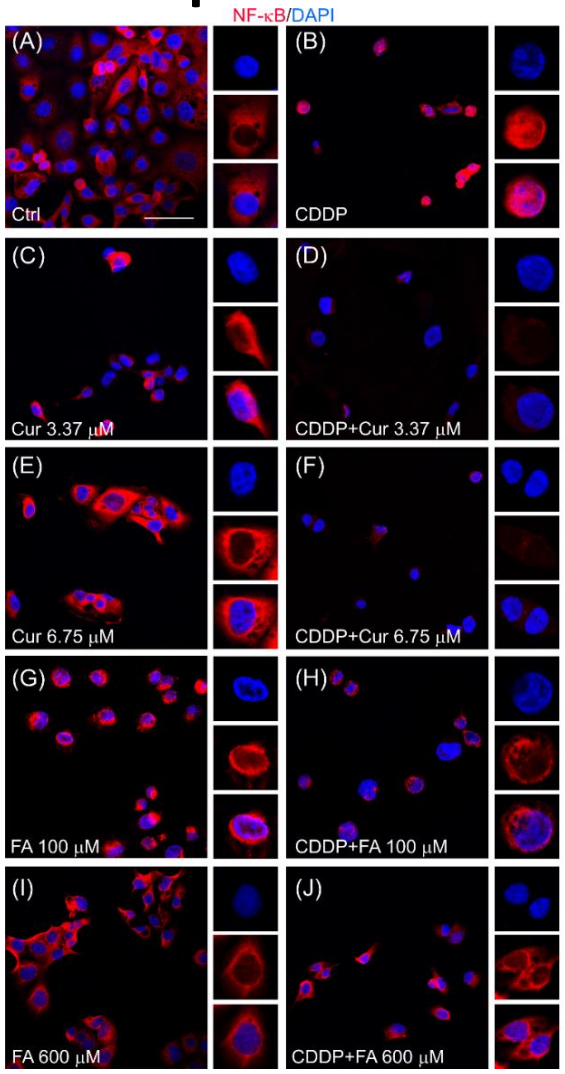


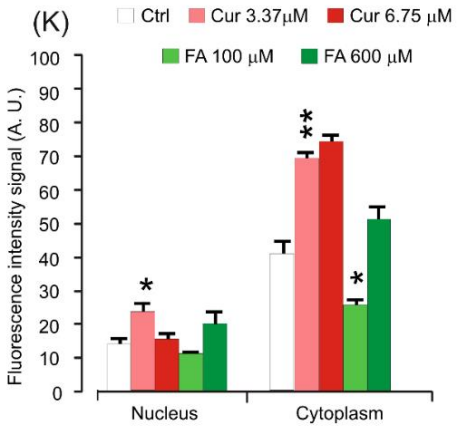


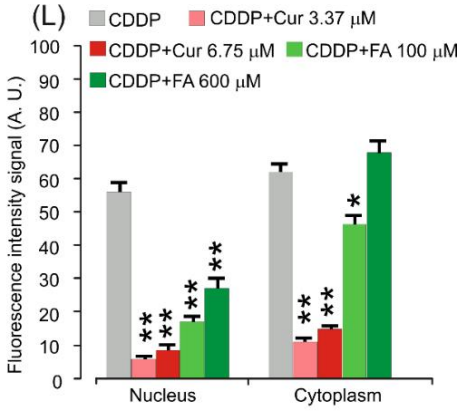
Reduce the p53 mediated inflammatory response

Fetoni et al, BJC 2015
Fetoni et al., Sci Rep 2020

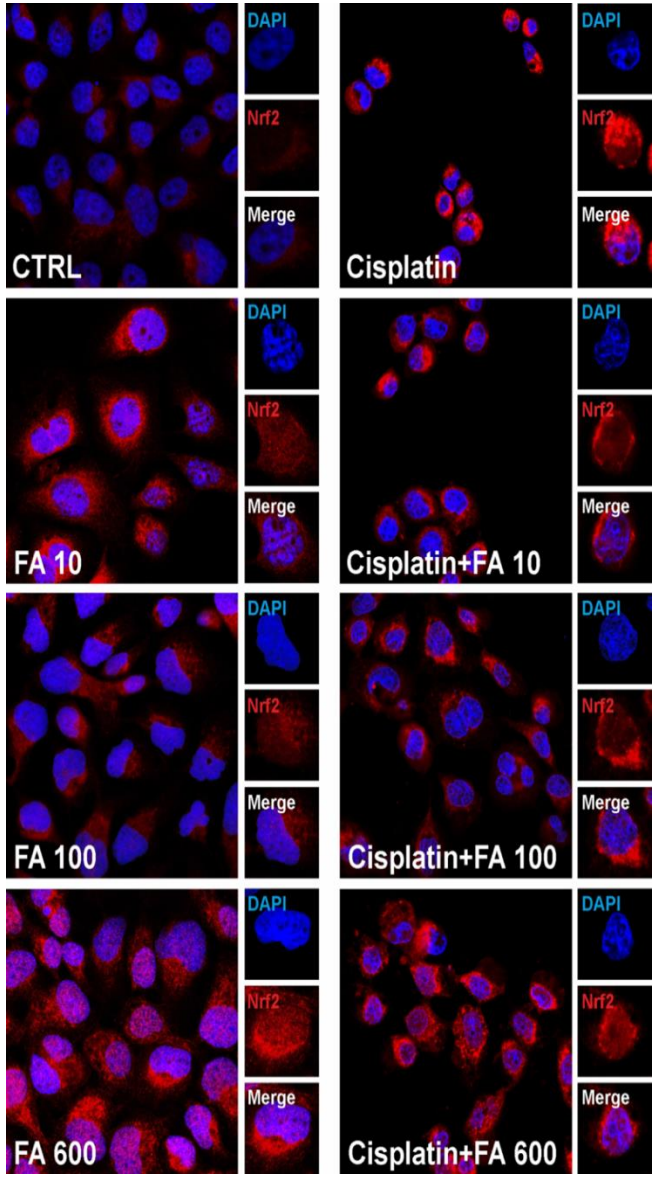
Curcumin decrease nuclear NF-κB expression in cancer cells enhancing antineoplastic effects

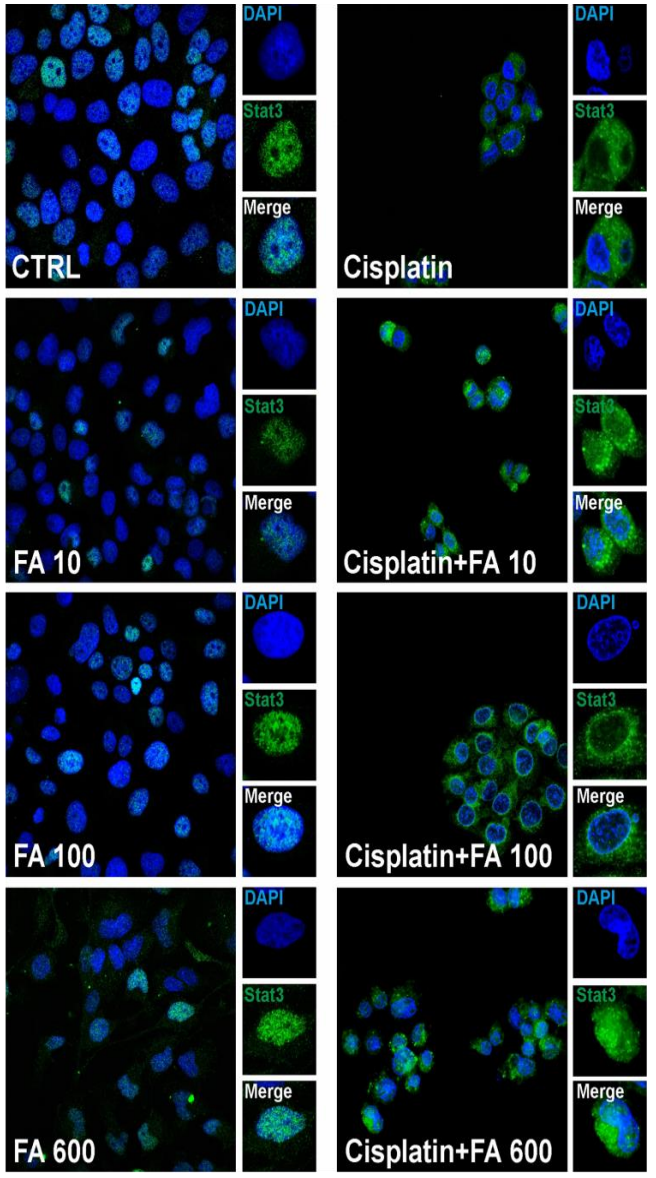


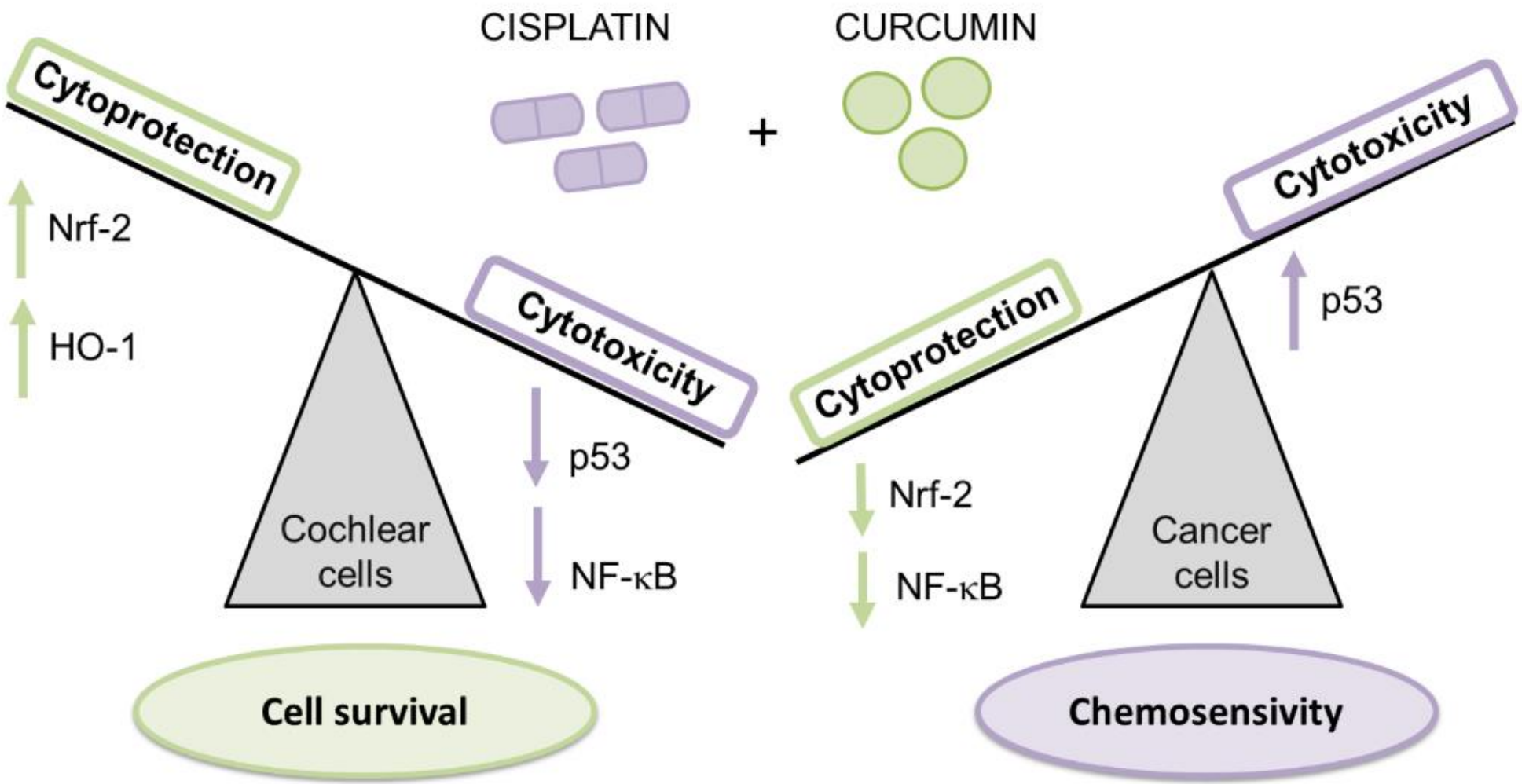




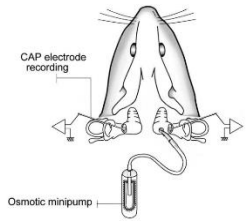
Ferulic Acid increases the translocation of Nrf2 e pSTAT3 increasing cisplatin chemoresistance

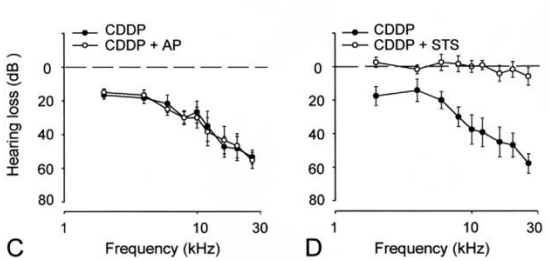


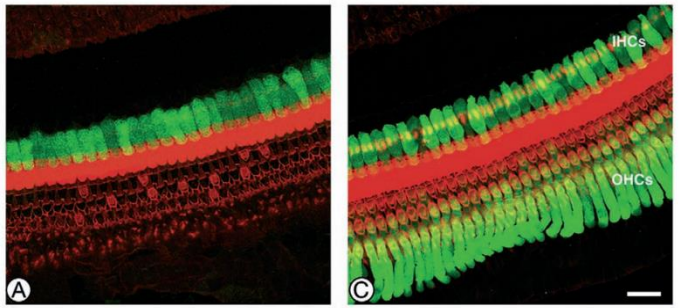



CISPLATIN
CURCUMIN
+
Cytoprotection
Nrf-2
HO-1
Cytotoxicity
p53
NF-κB
Cochlear cells
Cell survival
Cytoprotection
Nrf-2
NF-κB
Cytotoxicity
p53
Cancer cells
Chemosensivity

From experimental to clinical model: Sodium thiosulfate







(Wang & Fetoni Neuropharmacology 2003)

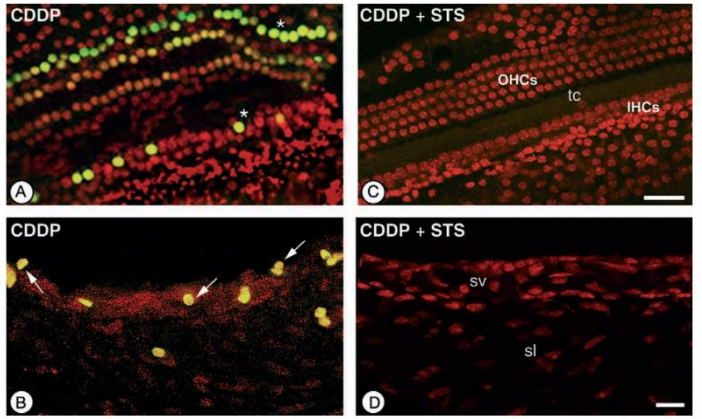


TABLE 1. Recommendations for enabling STS use in clinical practice

Recommendations for Clinical Practice	References
• Use STS in all cisplatin-treated children with localized disease.	Freyer et al. 2017; Brock et al. 2018
• Adjust all cisplatin infusion times to a maximum of 6 hr to enable STS administration.	Doolittle et al. 2001; Erdlenbruch et al. 2001; Moke et al. 2021
• Optimize the use of multiagent antiemetics to prevent nausea associated with STS administration.	Freyer et al. 2017; Brock et al. 2018; Patel et al. 2022
• No other systemic drug with comparable efficacy to STS is available to date.	Dickey et al. 2004; Dickey et al. 2005; Katzenstein et al. 2009; Muldoon et al. 2015; Fernandez et al. 2020; Fernandez et al. 2021; Orgel et al. 2023
• No alternative route of administration offers comparable efficacy to systemic administration to date.	Streefkerk et al. 2025

STS, sodium thiosulfate.

STREEFKERK ET AL. / EAR & HEARING, VOL. XX, NO. XX, 00–00

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

OPEN

Avoiding Cisplatin-Related Hearing Loss, Including Implementing Sodium Thiosulfate as Otoprotectant Into Daily Pediatric Clinical Practice: Proceedings Based on Evidence and Expert Opinion From the Ototoxicity Taskforce of the *SIOP Supportive Care Network*

TABLE 3. General considerations for cisplatin administration and for STS administration

A. Cisplatin administration

Consider the following when possible:

1. Avoid concurrent radiotherapy, and where possible give radiotherapy after the end of cisplatin administrations.
2. Avoid concurrent diuretics (e.g., furosemide)
3. Avoid concurrent aminoglycosides/glycopeptides (e.g., vancomycin)
4. Avoidance of vincristine infusion on the same day as cisplatin may reduce enhancing cisplatin-associated ototoxicity

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

Discussion

- High prevalence (>25%)
- Additive effect of radiotherapy (brain tumors)
- Long-term progression

- Need for Audiological FU
- Need for Prevention
- Need for a strict integration between professionals

Improving paediatric cancer care and defining audiological monitoring pathways

CULTURE and EDUCATION

Importance of continuing the discussion on cisplatin-induced ototoxicity, thus expanding knowledge on the topic

MULTI-DISCIPLINARY SHARING AND COLLABORATION.

Importance of strengthening collaboration between ENT and paediatric oncologist with a view to defining an integrated care pathway

STANDARDIZATION and DEFINITION OF ORGANIZATIONAL MODELS.

Importance of defining monitoring models (such as audiometric examinations, frequency, how to structure long-term follow-up to assess the possible evolution of hearing damage) that can be shared in a wider number of centers


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