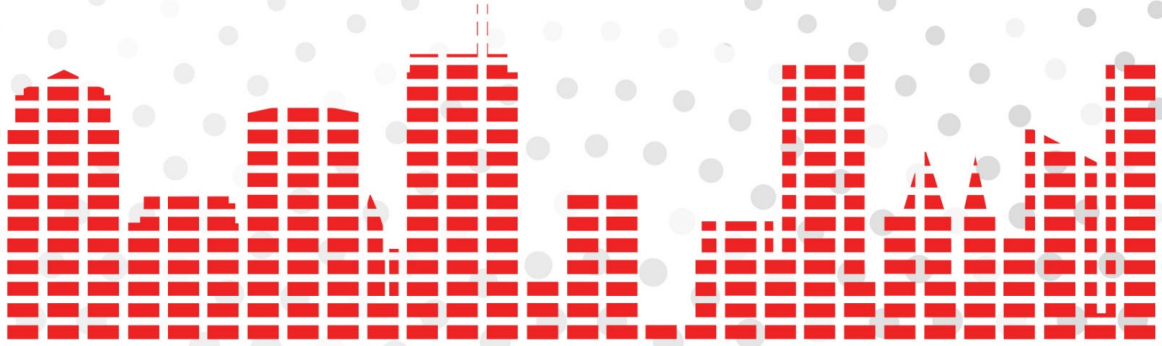

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Cancer, Treatment and Ototoxicity

Michelle McElhannon, PharmD
The University of Georgia College of Pharmacy

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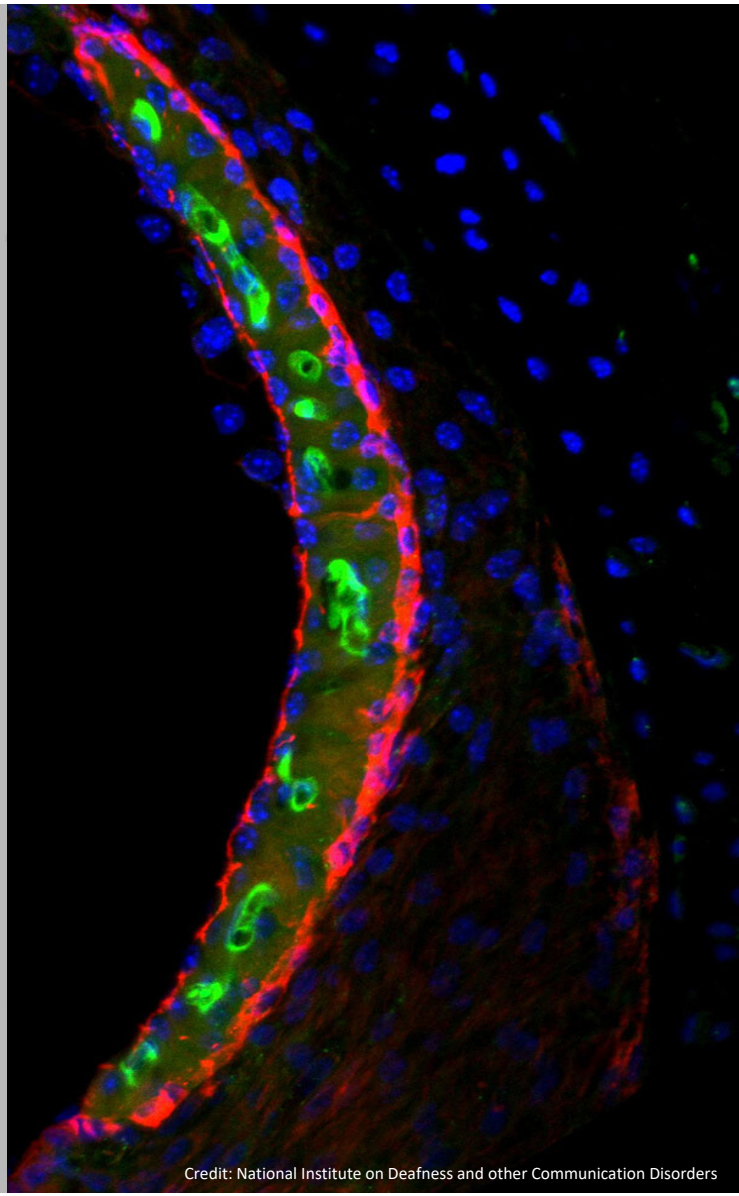
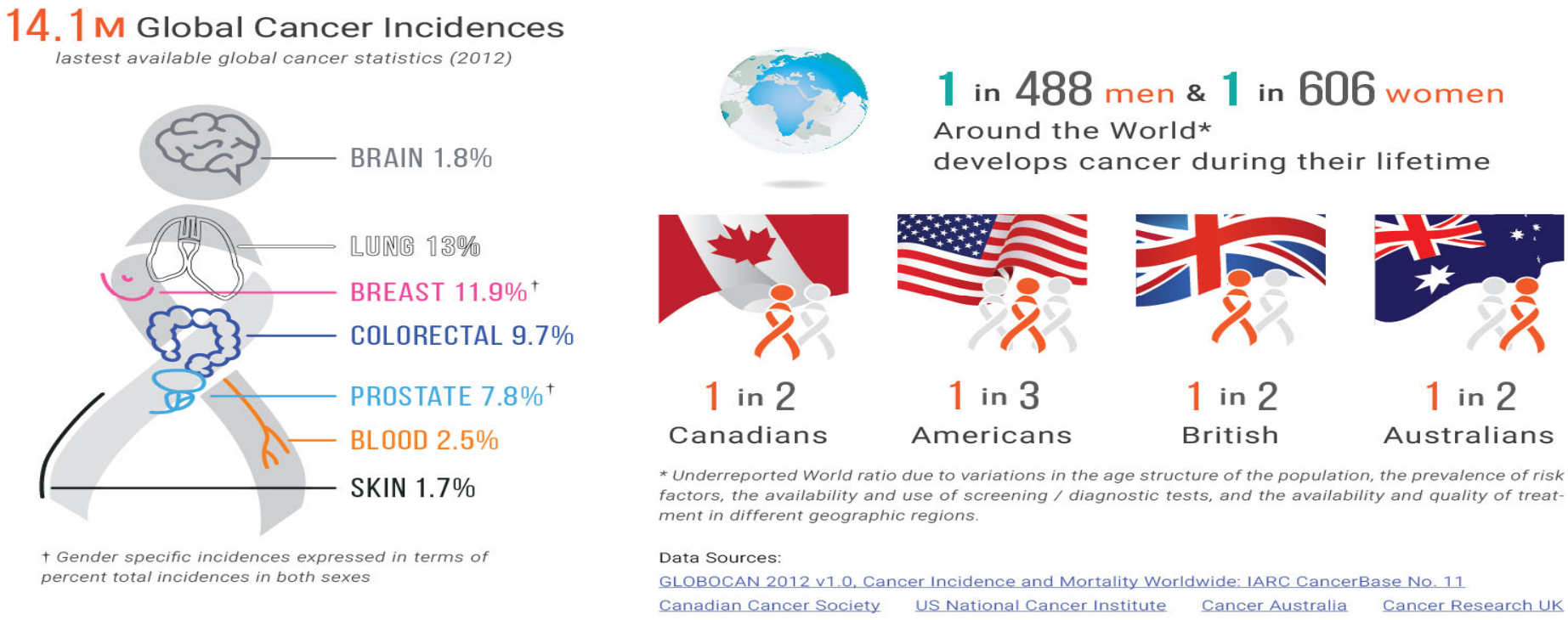


Credit: National Institute on Deafness and other Communication Disorders

Objectives

- Discuss the pathogenesis of cancer
- Examine the goals of treatment and mechanisms of action of anti-neoplastic therapies
- Explain cancer and treatment-induced ototoxicities
- Explore preventative therapies in development
- Offer Co-management strategies

Incidence

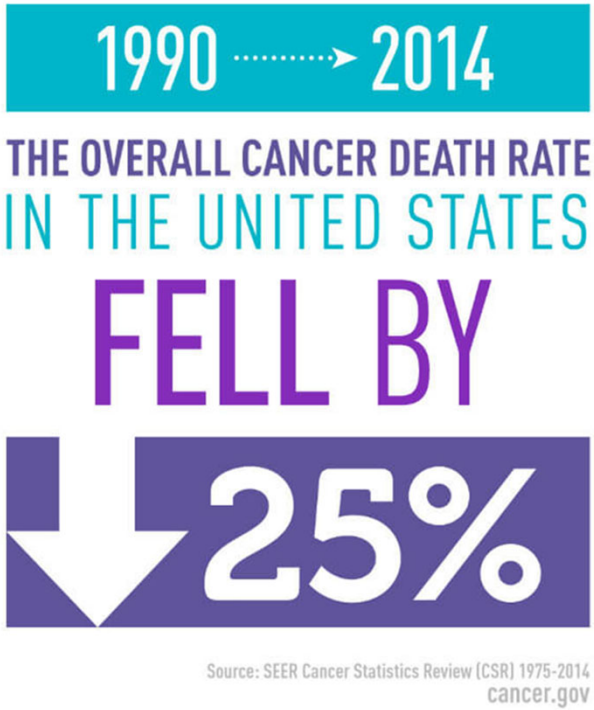


- Approximately 38.4% of men and women will be diagnosed with cancer during their lifetimes.

https://www.cancer.gov/about-cancer/understanding/statistics

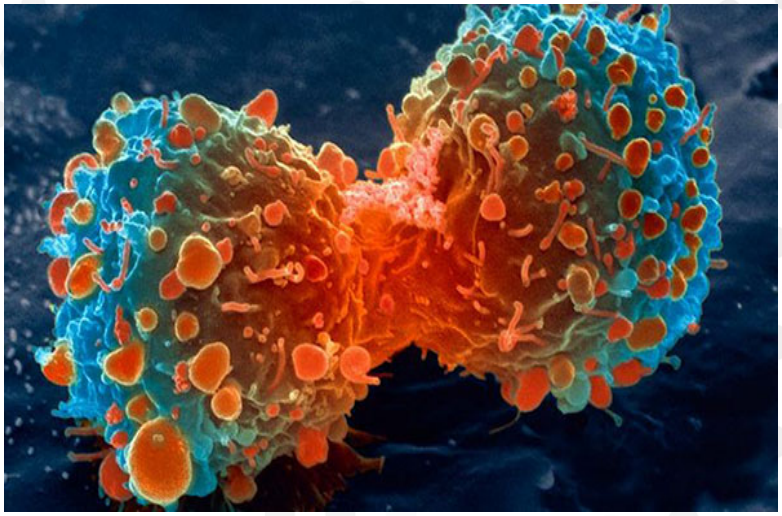
Progress

- In 2016:
  - Estimated 15.5 million survivors in the U.S.
- By 2026:
  - Estimated to increase to 20.3 million



What is Cancer?

- Cells begin to divide without stopping and spread into the surrounding tissues
- Old or damaged cells survive, and new cells form when they are not needed
- Cancer cells are less specialized than normal cells
- Cancer cells can ignore signals for apoptosis

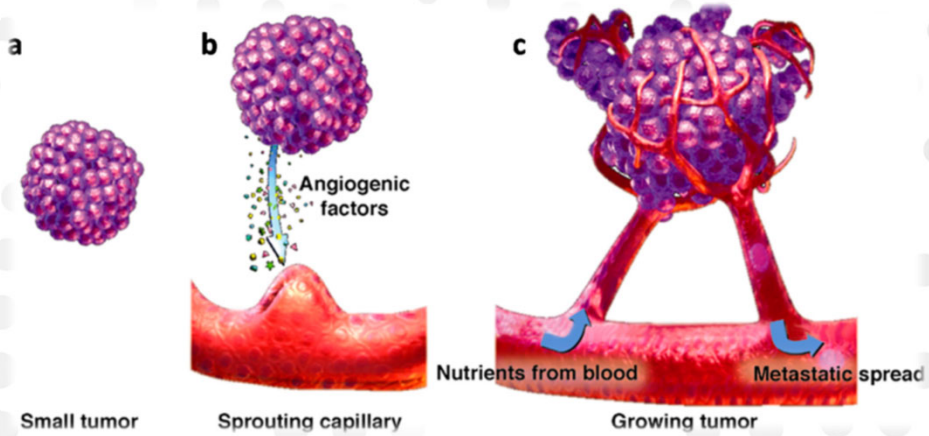


A dividing lung cancer cell
Credit: National Institutes of Health

https://www.cancer.gov/about-cancer/understanding/what-is-cancer; "What is Cancer?" was originally published by the National Cancer Institute

Cancer

- Cancer cells may influence normal cells, molecules and blood vessels to supply tumors with nutrients and remove waste
- May evade the immune system
- Cancer cells have more genetic changes, or mutations, than normal cells



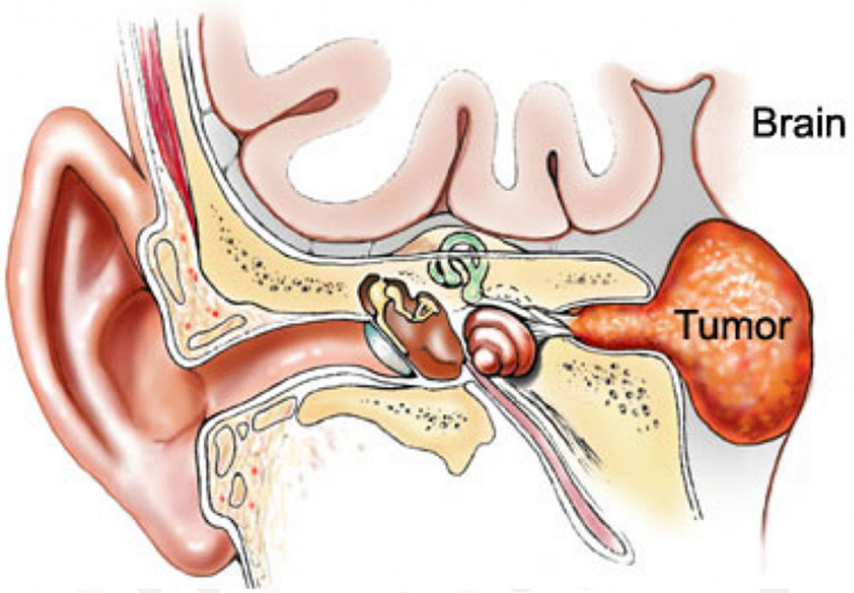
https://www.mdpi.com/1422-0067/18/9/1967

Neoplastic treatments

- Surgery
- Radiation
- Chemotherapy
- (Immunotherapy)

Surgery

- Tumors may place pressure or infiltrate
- Surgery may further damage the ear and auditory nerve
- Central nervous tumors may cause rapid changes in intracranial pressure
  - Lumbar puncture, tumor resection, ventriculostomy
- Cerebral spinal fluid shunts



Radiation

- Radiation therapy uses high-energy particles or waves, such as x-rays, gamma rays, electron beams, or protons, to destroy or damage cancer cells.
- Radiation causes small breaks in the DNA inside cells, which keep cancer cells from growing and dividing and causes cell death.

- Usually local treatment
- External beam radiation
  - High energy rays
- Internal radiation, or brachytherapy
  - Radioactive source placed in or near the tumor
- Systemic radiation
  - IV or by mouth

Radiation-induced ototoxicity

- Dose related
  - >30 grays
- Risks increased with multimodality therapy
- Sensorineural loss is generally permanent and progressive
- Onset may be acute or delayed

- Posterior nasopharynx and mastoid
  - Serious otitis media, conductive hearing loss
- External auditory canal
  - Soft tissue infections
  - Increased cerumen production/dry cerumen
- Cochlea
  - Sensorineural hearing loss
- Brainstem
  - Indirect

Radiation-induced ototoxicity

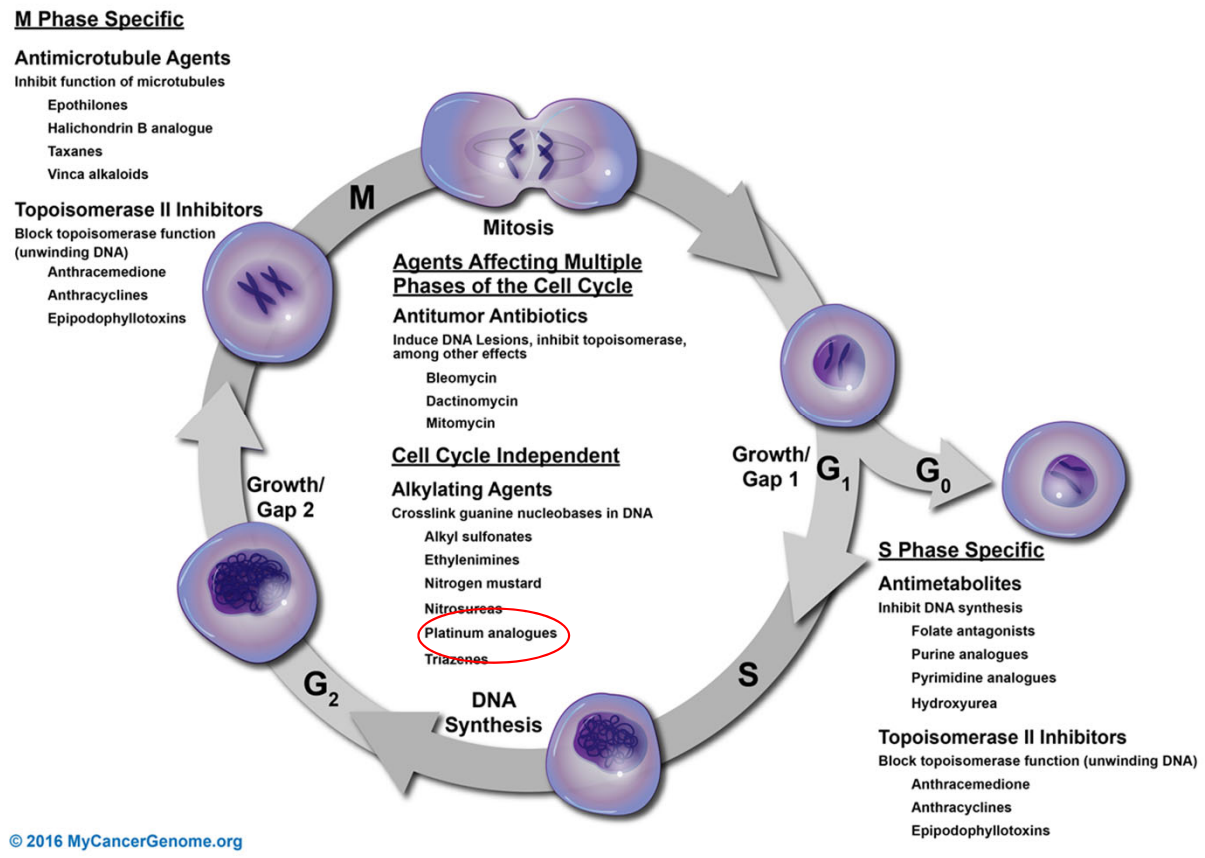
- Senorineural: Hearing loss affects 1/3 of patients
- Typically late onset, 3-5 yrs post-tx
- Irreversible
- Progressive
- More severe in the high frequencies
- Poor word discrimination common

- Points
  - Cumulative cochlear mean dose <35 Gy should be considered for patients receiving 54-59.4 Gy in 30-33 treatment fractions
  - Followup with prospective testing through 10 years following CRT

Jereczek-Fossa et al., 2003; Ho et al 1999; Hua et al, 2008

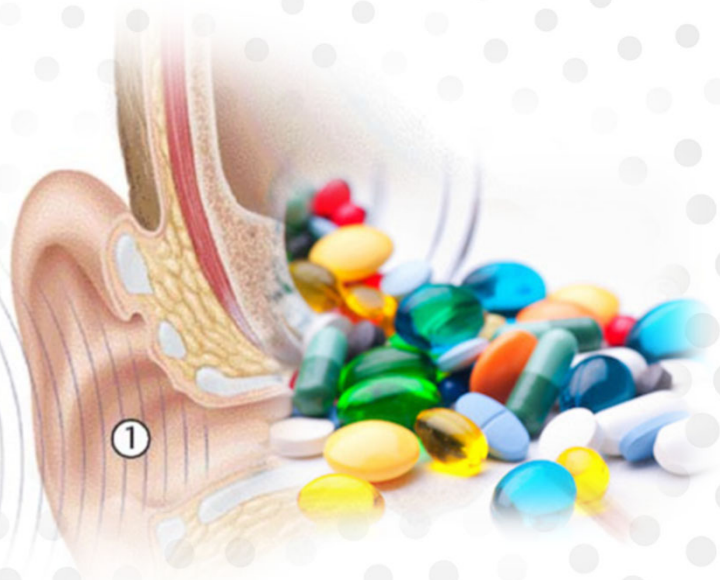
Chemotherapy

- The cell cycle goes from the resting phase, through active growing phases, and then to mitosis (division)
- The ability of chemotherapy to kill cancer cells depends on its ability to halt cell division.
- Usually, cancer drugs work by damaging the RNA or DNA that tells the cell how to copy itself in division.



Drug-induced ototoxicity

- Susceptibility of the tissue to the drug
- Accumulation of the drug within the organ
- Inhibition of normal physiologic functions
- Direct toxic effects on the sensory end organs
- Central effects
- Ototoxic synergism



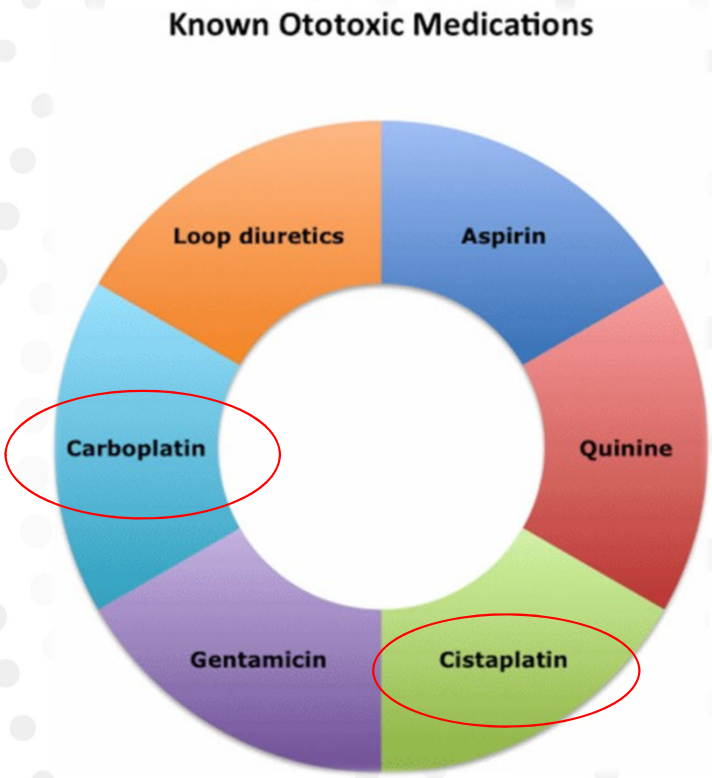
Ototoxicity of chemotherapy and adjunct agents: patient risk factors

- Age
  - <5yrs old or >46 yrs old
- Co-morbid conditions
  - Congestive heart failure
  - Renal failure
  - Hypertension
- Dehydration
- Genetic

- High dose
  - Cisplatin: cumulative >400 mg/m^2
- Increasing number of cycles
- Co-administration of other ototoxic agents
- Concurrent or past cranial irradiation

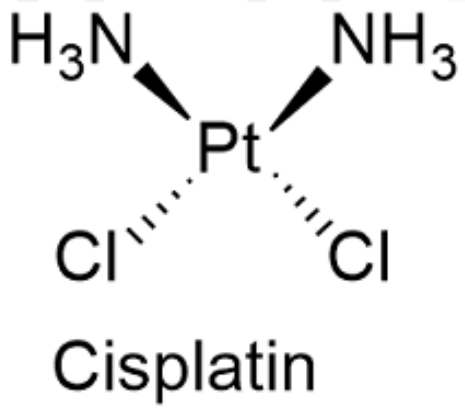
Ototoxicity of chemotherapy and adjunct agents

- Antineoplastic:
  - Cisplatin, Carboplatin
  - Nitrogen mustard
  - Methotrexate
  - Vincristine
  - Dactinomycin
  - Bleomycin



Chemotherapy

- Platinum-based
  - Cisplatin, Carboplatin, Oxaloplatin
  - Solid tumors of head, neck, lung, ovary, testicle and bladder in adults
  - Neuroblastoma, osteosarcoma, hepatoblastoma, germ cell and CNS tumors in children
- MOA
  - Free-radical production

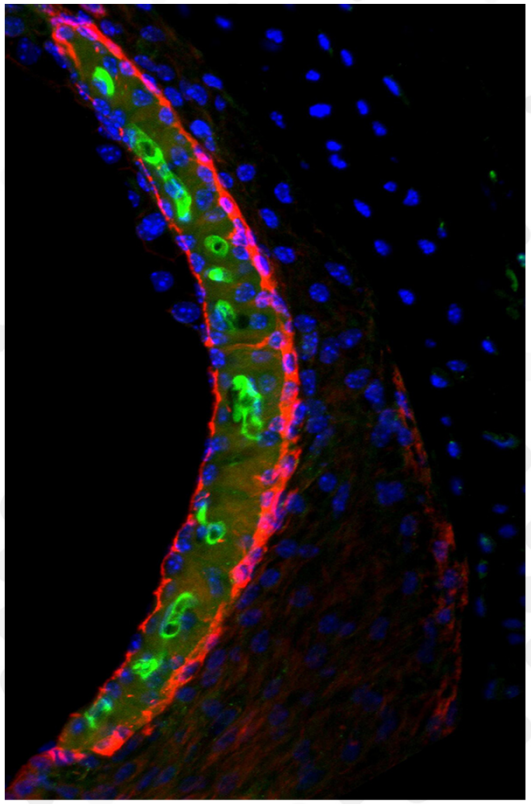


Cisplatin

Cl ions get exchanged by water molecules, becoming a highly reactive aquo complex. Binds to nucleophiles in DNA, RNA, Proteins and peptides. Blocks DNA replication, transcription,Respiration and induces ROS= cell death.

Cisplatin

- Ototoxicity
  - Occurs 23-50% in adults
  - Occurs 22-77% in children
- Eliminated days to weeks from other organs
- Increased time of exposure in the cochlea, accumulates in the stria vascularis- retained for months to years after treatment

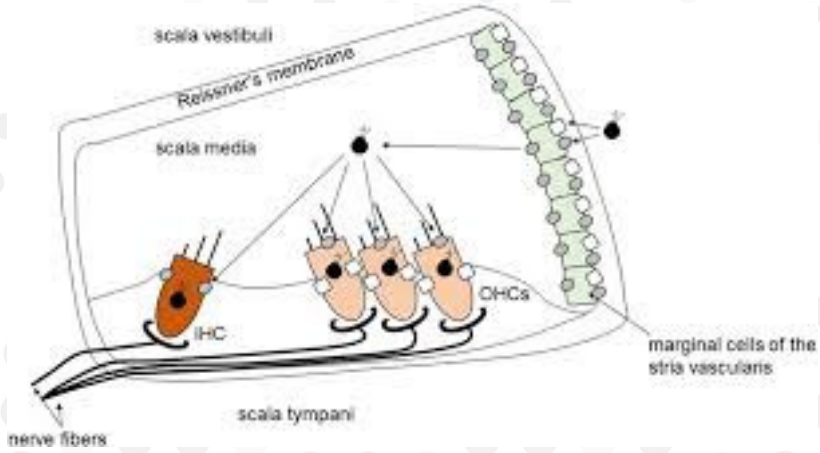


Cisplatin (green) in a mouse inner ear

Credit: National Institute on Deafness and other Communication Disorders

Cisplatin

- OHCs of basal part of the cochlea are initially affected
  - Observed hearing impairment at high frequencies
- With continued treatment, damage progresses to medial and apical cochlear OHCs and to the IHCs
  - Lower frequencies
  - Speech frequencies



Cisapride, Copper transporter 1, Organic cation transporter 2

OHC= Outer Hair Cells; IHC= Inner Hair Cells

Lanvers-Kaminsky , C., Zehnhoff-Dinnesen, A., Parfitt, R. et al. Clin Pharm. Ther 101(4):491-500 (2017)

Characteristics of cisplatin ototoxicity

- Research shows that every 100mg/m2 increase in cumulative dose resulted in a 3.2 dB hearing impairment
- Presentation
  - Tinnitus
  - Hearing loss
  - Hyperacusis
  - Aural fullness
  - Dizziness
  - Vertigo
- Onset
  - Simultaneous or singular
  - Rapidly or gradually
- Duration
  - Reversible or Irreversible
- High blood pressure is related to hearing loss with cisplatin

Frisna, R., Wheeler, H., Fossa, S., et al. J Clin Oncol 2016 **34**:23, 2712-2720

Adjunct ototoxic therapies

Aminoglycosides

- Irreversible
- Decreased clearance from inner ear fluids
  - Single dose $t_{1/2}$=10-13 days
  - Multiple dose $t_{1/2}$= up to 30 days
- Damage to cochlear hair cells, stria vascularis, marginal cells and the spiral ganglion
- ROS, mitochondrial
- Genetics
  - A1555G mutation, codes for mitochondrial 12S rRNA. Mutated 12S rRNA resembles bacterial 16S rRNA

Differing ototoxic properties:

	Vestibulotoxic	Cochleotoxic
Neomycin		XXX
Gentamicin	XX	Xx
Kanamycin		Xx
Tobramycin	X	X
Streptomycin	XX	
Amikacin		X

Xie, J., Talaska, A., Schacht, J. Hear Rs 281, 28-37 (2011)
Hain, T.C. <Http://www.dizziness-and-balance.com/disorders/bilat/PCD.html>

Aminoglycoside Points:

Aminoglycosides

- Careful monitoring of serum concentration
- Renal function
- Once daily dosing best
- Hearing evaluation
  - Before, during, after therapy
- Avoid noisy environments for 6 months after therapy

Potential Otoprotectants

- Antioxidant N-acetyl-cysteine
- Vit E
- Alpha lipoic acid
- Ebselen
- Ginkgo biloba

Adjunct ototoxic therapies

Loop diuretics

- Furosemide, bumetanide, ethacrynic acid, torsemide
  - Reversible, self-limiting
  - Irreversible reports in neonates
- Changes in the ionic gradients between perilymph and endolymph
  - Causing edema of the epitheoium of the stria vascularis
- Blood flow reduction impairs the barrier function of the endothelium
  - Allows entry of other ototoxic drugs.

Loop Diuretic Points:

- Use lowest possible dose
- Avoid rapid infusion rates
- Avoid co-administration of other ototoxic agents
- Caution in patients with renal failure

Chemo-induced ototoxicity prevention strategies

Challenge

- Protection from the cytoxic effect on the cells of the ear may decrease the cytoxic effect on cancer cells, and impair anti-tumor activity
  - Free radical scavengers, antioxidants
- Agent must cross the blood inner-ear barrier or diffuse through the round window membrane

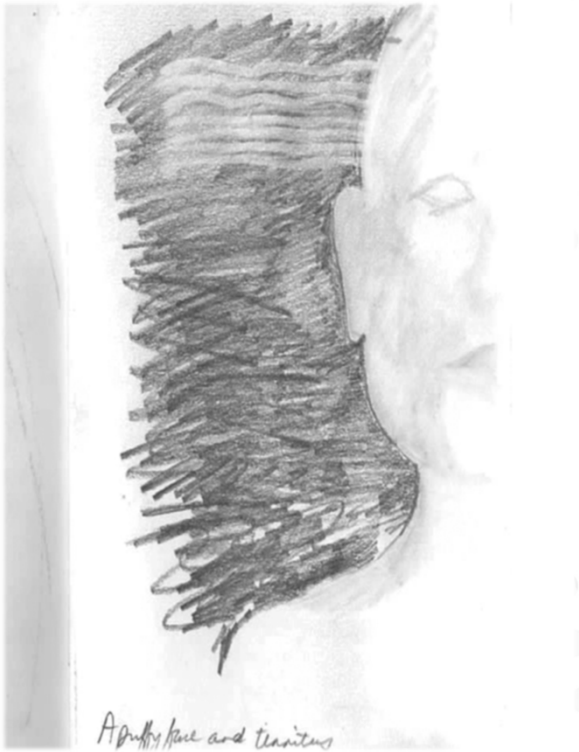
Problem-solving

- Preclinical evaluation of tumor cell transport expression
  - Lack of OCT2 expression in pediatric tumor types
- Intratympanic administration
  - Selective

Otoprotectants in studies

- Endogenous production of anti-oxidants
  - Sodium thiosulfate
  - D-methionine
  - Ebselen
- Free Radical Scavengers
  - Amifostine
- Antioxidants
  - N-acetylcysteine
  - Vit E
- ROS production prevention
  - Allopurinol
  - Erdosteine
- Inhibition of transporters
  - OCT2
  - CRT1

Monitoring/Co-management

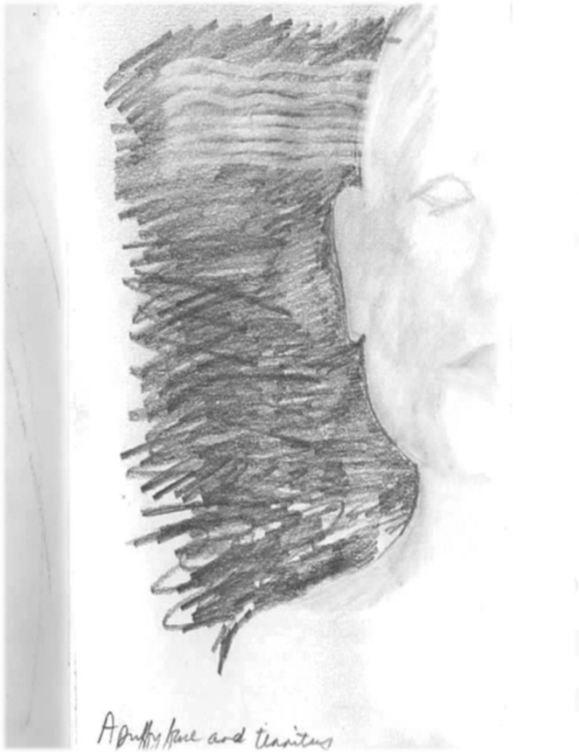


Interdisciplinary communication:

Patients usually do not know what chemotherapy they are taking.

- Platinol®, Platinol®-AQ, CDDP
- CT: Cisplatin/topotecan
- Herceptin®: Cisplatin/ capecitabine/trastuzumab
- Gemzar®: Cisplatin/gemcitabine
- Taxotere®: Cisplatin/docetaxel

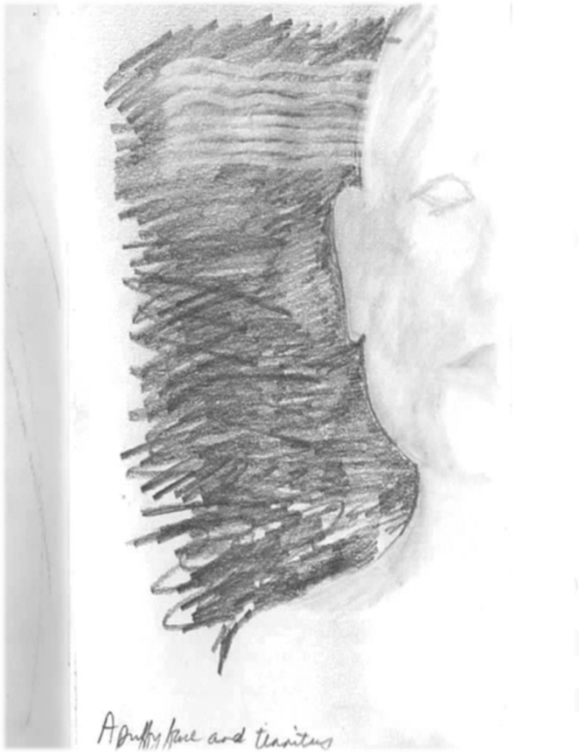
Monitoring/Co-management



Patient counseling:

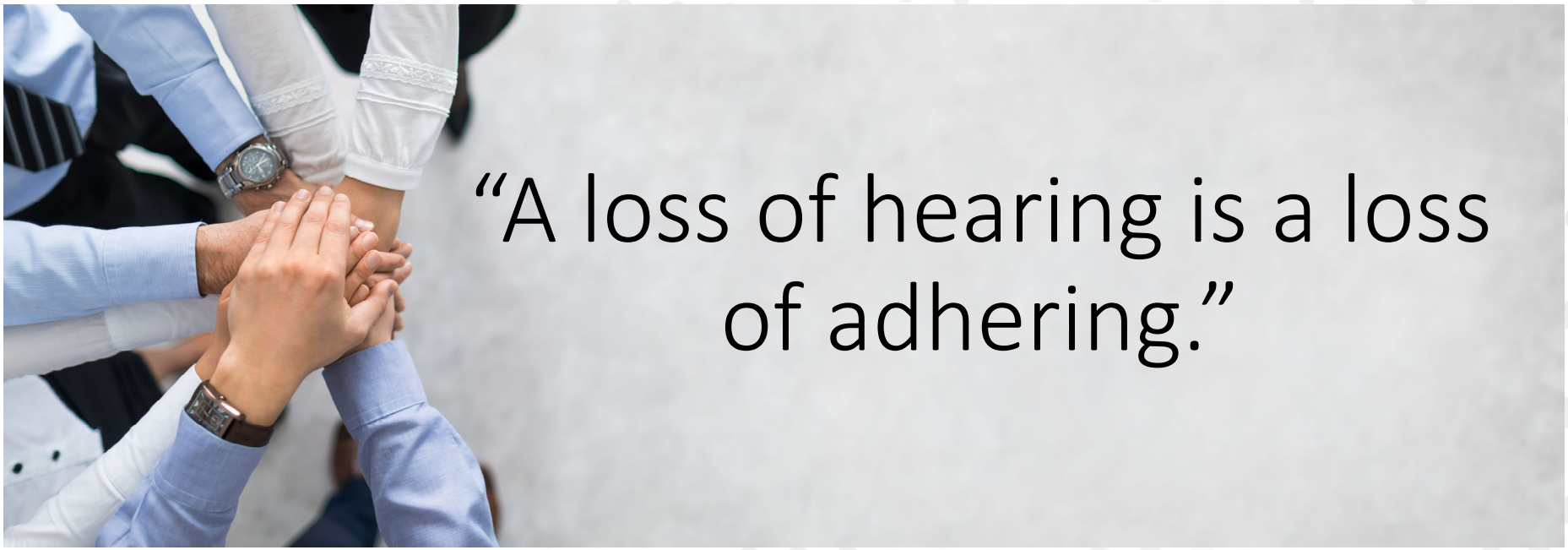
- Signs and symptoms of cochlear damage and potential effects on communication ability
- Symptoms such as tinnitus, fullness, loss of balance, or changes in hearing sensitivity
- Potentiating effects such as exposure to noise during or following treatment
- If the patient lives or works in an environment with high noise levels, the possible synergistic effect of noise and cochleotoxic damage must be considered, and both the patient and family should be made aware of this increased risk
- Audiological followup may be required long-term

Monitoring/Co-management



Pearls

- High blood pressure can worsen cisplatin-induced ototoxicity
- Dehydration increases ototoxic risk
- Cisplatin is also nephrotoxic, increasing ototoxic potential further
- Radiation in conjunction with chemotherapy can worsen the risk of ototoxicity
- List and screen other medications for additive ototoxic and nephrotoxic potential


“A loss of hearing is a loss of adhering.”

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