Alkylating agents

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Procarbazine

- Chemical class methyl hydrazine
- Hepatic oxidative metabolism convert procarbazine into different metabolites. One form is azo-procarbazine which methylate DNA.
- One of the other metabolite is weak monoamine oxidase inhibitor.
- It is monofunctional methylating agent and has greater capacity to cause muta and carcino-genecity.

Procarbazine

- Activated procarbazine can produce chromosomal damage, including chromatid breaks and translocations.
- Resistance to procarbazine develops rapidly when it is used as a single agent.
- it is used in combination regimens (MOPP) for Hodgkin's and non-Hodgkin's lymphoma as well as brain tumors.

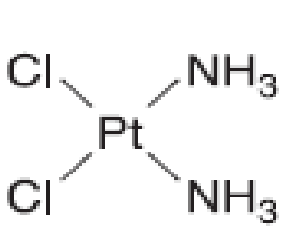
Procarbazine

- Procarbazine should be given carefully with other MAO inhibitors as well as with sympathomimetic agents, tricyclic antidepressants, antihistamines, central nervous system depressants, antidiabetic agents, alcohol, and tyramine containing foods.
- There is an increased risk of secondary cancers in the form of acute leukemia.
- Other toxic effects include thrombocytopenia, nausea and vomiting.

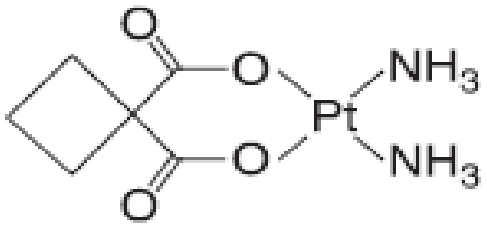
Platinum compounds

- Cisplatin
- Oxaliplatin
- Carboplatin
- Cisplatin was the first FDA-approved platinum compound for cancer treatment in 1978 .
- Platinum compounds have become the foundation for treatment of ovarian, head and neck, bladder, esophagus, lung, and colon cancers.
- Cisplatin and carboplatin are divalent, inorganic, water soluble platinum-containing complexes. Oxaliplatin is a tetravalent complex.

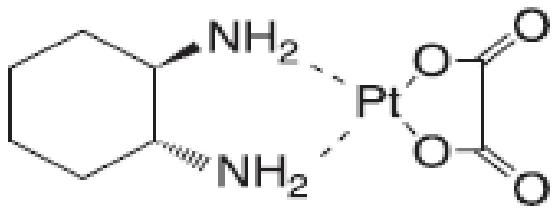
Platinum compounds.....



CISPLATIN



CARBOPLATIN

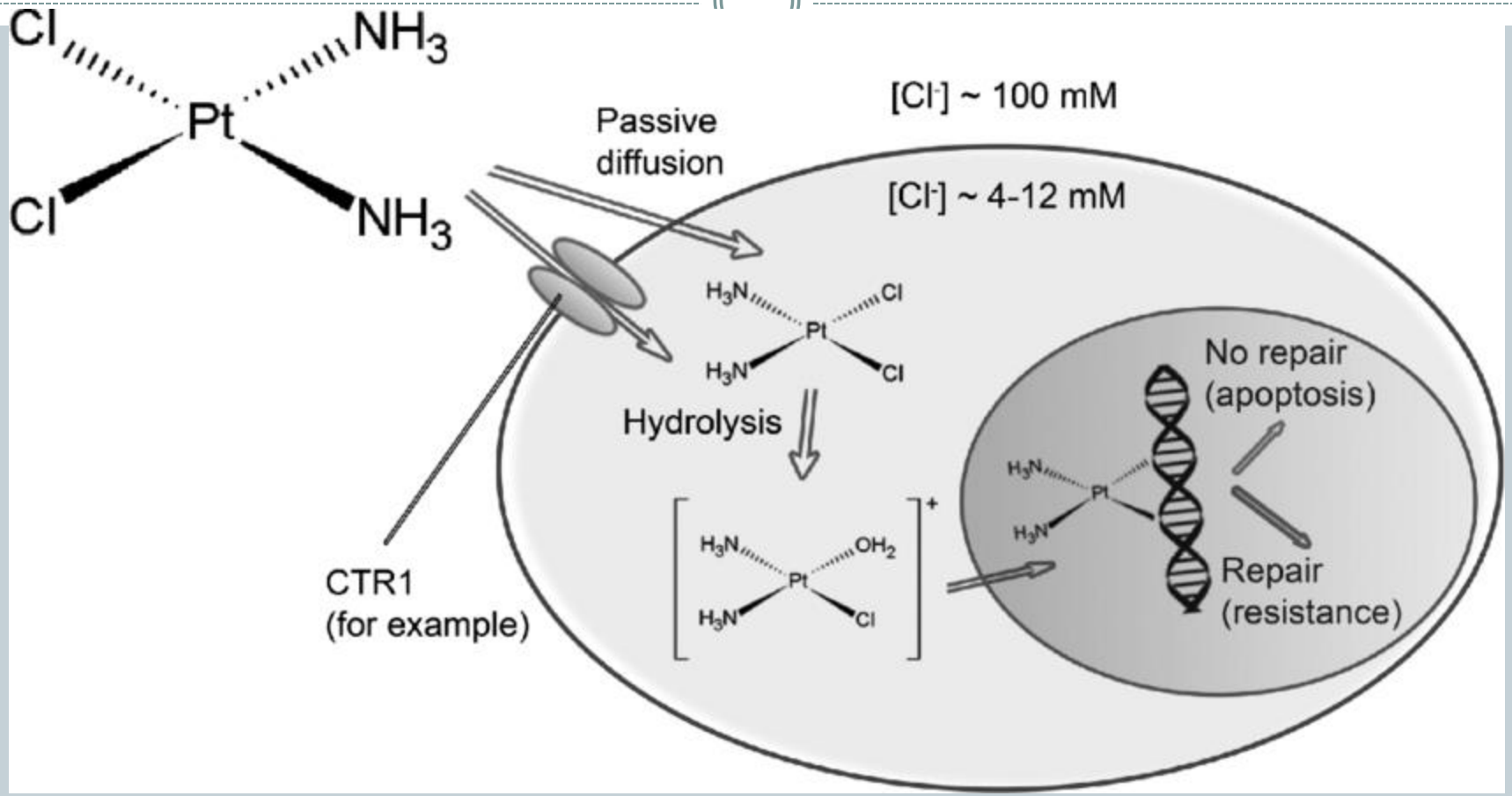


OXALIPLATIN

Platinum compounds.....

- Cisplatin, carboplatin, and oxaliplatin enter cells by an active Cu2+ transporter (CTR1).
- Inside the cell, the chloride, cyclohexane, or oxalate ligands of the three analogs are displaced by water molecules, yielding a positively charged and highly reactive molecule.
- In the primary cytotoxic reaction, the aquated species of the drug then reacts with nucleophilic sites on DNA and proteins.

Mechanism of action



Platinum compounds.....

- The activated platinum complexes can react with electron-rich molecules, such as sulfhydryls, and with various sites on DNA, forming both intrastrand and interstrand cross-links.
- The N-7 of guanine is a particularly reactive site, leading to platinum cross-links between adjacent guanines (GG intrastrand cross-links) on the same DNA strand.

Platinum compounds.....

- Cisplatin, among others, attacks mitochondria and triggers the production of ROS, destroys lysosomes inducing the release of lysosomal proteases and degrades endoplasmic reticulum which results in the deregulation of calcium storage and in the misfolded proteins.
- Beside the DNA in mitochondria, cisplatin attacks other organelles by forming adducts with functional groups on proteins, especially with the sulphur atom in cysteine and methionine side chains.

Therapeutic uses

- Cisplatin, in combination with bleomycin, etoposide, ifosfamide, or vinblastine, cures 90% of patients with testicular cancer (Combination is effective to prevent resistance).
- With paclitaxel, cisplatin or carboplatin induces complete response in the majority of patients with carcinoma of the ovary.
- Cisplatin produces responses in cancers of the bladder, head and neck, cervix, and endometrium; all forms of carcinoma of the lung; anal and rectal carcinomas; and neoplasms of childhood.
- The drug also sensitizes cells to radiation therapy and control of locally advanced lung, esophageal, and head and neck tumors when given with irradiation.

Platinum compounds.....

- Carboplatin and cisplatin are equally effective in the treatment of ovarian cancer, non–small cell lung cancer, and extensive-stage small cell lung cancer.

- However, carboplatin may be less effective than cisplatin in germ cell, head and neck, and esophageal cancers.

Platinum compounds.....

- Toxicities:
- Nephrotoxicity
- Ototoxicity
- Nausea and vomiting
- Peripheral motor and sensory neuropathy (Oxaliplatin)
- Mild to moderate myelosuppression
- Electrolyte imbalance
- Carboplatin is relatively well tolerated clinically, causing less nausea, neurotoxicity, ototoxicity, and nephrotoxicity than cisplatin.