Platinum Analogs Pharmacology

The platinum analogs (**cisplatin, carboplatin**) covalently bind to the DNA and work nonspecifically regarding the cell cycle. These drugs are used in the treatment of a number of tumors such as non-small cell lung cancer, small cell lung cancer, carcinoma of the head and neck, esophageal cancer, bladder cancer, ovarian cancer, germ cell carcinoma, non-Hodgkin's lymphoma).

They work by enhancing the tumor activity of etoposide and are widely used (cisplatin) as radiosensitizers.

Amifostine and **mesna** may ameliorate the nephrotoxicity.

There are three platinum analogs that are used clinically and these are;

1. **Cisplatin,**
2. **Oxaliplatin and**
3. **Carboplatin**

Cisplatin (cis-diamminedichloroplatinum)

Cisplatin is an inorganic metal complex discovered through the serendipitous observation that neutral platinum complexes inhibited division and induced filamentous growth of Escherichia coli.

Cisplatin is thought to exert its **cytotoxic effects** in the same manner as alkylating agents.

It kills cells in all stages of the cell cycle, **binds DNA through the formation of intrastrand and interstrand cross-links, and inhibits DNA synthesis and function**.

The primary binding site for cisplatin is the **N7 position of guanine**, but covalent interaction with adenine and cytosine also occurs.

The platinum complexes appear to **synergize** with certain other anticancer drugs. **Aggressive hydration with intravenous saline infusion** has been shown to significantly reduce the incidence of nephrotoxicity.

Cisplatin has major antitumor activity in a broad range of solid tumors, including

? non-small cell and small cell lung cancer,
? esophageal and gastric cancer,
? head and neck cancer, and
? genitourinary cancers, particularly testicular, ovarian, and bladder cancer.

When used in combination regimens with vinblastine and bleomycin or etoposide and bleomycin, cisplatin-based therapy has led to the cure of nonseminomatous testicular cancer.

Acute toxicity associated with cisplatin is nausea and vomiting and chronic toxicities associated

with this drug are **nephrotoxicity**, **peripheral sensory neuropathy, ototoxicity and nerve dysfunction.**

Cisplatin is typically administered intravenously over 1 or more hours.

Mechanism of Action

Cisplatin is a platinum coordination compound that inhibits DNA synthesis; cross-links and denatures strands of DNA; disrupts DNA function by covalently binding to DNA bases; can also produce DNA intrastrand cross-linking and breakage

It is not a true alkylating agent

Pharmacokinetics

It has an elimination half-life of 24hr to 47 days

Protein bound: >90%

Excretion: Urine (90%); feces (10%)

Clearance: 15 L/hr/m²

Vd: 11 L/m²

Carboplatin

Carboplatin is a second-generation platinum analog that exerts its cytotoxic effects exactly as cisplatin and has activity against the same spectrum of solid tumors.

Its main dose-limiting toxicity is **myelosuppression**, **hepatic dysfunctionn and** it has significantly less renal toxicity and gastrointestinal toxicity than cisplatin.

Intravenous hydration is not required, and for this reason, carboplatin has now widely replaced cisplatin in combination chemotherapy regimens.

Mechanism of Action

Carboplatin is a platinum coordination compound; covalently binds to DNA; cross-links strands of DNA

It is also not a true alkylating agent

Absorption

Peak plasma time: 2-4 hr

Distribution

Protein bound: 87% (platinum)

Vd: 16 L

Elimination

Clearance: 4.4 L/hr

Excretion: Urine (70% as carboplatin)

Half-life

- Carboplatin: 3-6 hr
- Free ultrafilterable platinum: 6 hr
- Total plasma platinum: 4-6 days

Oxaliplatin

Oxaliplatin is a third-generation diaminocyclohexane platinum analog.

Its mechanism of action is identical to that of cisplatin and carboplatin. However, cancer cells that are resistant to cisplatin or carboplatin on the basis of mismatch repair defects are not cross-resistant to oxaliplatin.

This agent was originally approved for use as second-line therapy in metastatic colorectal cancer following treatment with the combination of 5-fluorouracil and leucovorin (5-FU/LV)—the FOLFOX regimen.

The FOLFOX regimen has now become the most widely used regimen in the first-line treatment of advanced colorectal cancer, and it is now widely used in the adjuvant therapy of stage III colon cancer.

Neurotoxicity is dose-limiting and characterized by a **peripheral sensory neuropathy and myelosuppression**.

There are two forms of neurotoxicity, an **acute form** that is often triggered and worsened by exposure to cold, and a **chronic form** that is dose-dependent.

Although this chronic form is cumulative in nature, it tends to be reversible, in sharp contrast to cisplatin-induced neurotoxicity.

Mechanism of Action

Oxaliplatin is a platinum coordination compound that inhibits DNA synthesis; cross-links and denatures strands of DNA; disrupts DNA function by covalently binding to DNA bases

Pharmacokinetics

Peak plasma time: 2 hr

Concentration: 1.21 mcg/mL

Protein bound: >90%; platinum accumulates in RBCs

Vd: 440 L

Half-life: 391 hr

Clearance: 10.1 L/hr

Excretion: Urine (54%); feces (2%)

This agent is not dialyzable.