Principles of Cancer Pharmacology

*A focused review of two major classes of **Cell-Cycle Non-Specific** chemotherapeutic agents: the Anthracyclines and the Platinum Analogs.*

Dr. Anup Ashokrao patil
Associate Professor
Department of Pharmacology
Krishna Institute of Pharmacy
Krishna Vishwa Vidyapeeth (Deemed to be University), Karad

Learning Objectives

1

Define CCNS vs. CCS Agents

Distinguish cell-cycle non-specific from cell-cycle specific agents and their clinical implications.

2

Describe Mechanisms of Action

Explain how anthracyclines and platinum analogs kill cancer cells at the molecular level.

3

Identify Clinical Uses & Toxicities

Recognize key indications and the major adverse effects of each drug class.

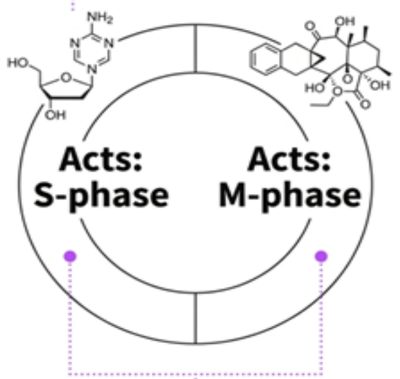
4

Dose-Limiting vs. Cumulative Toxicity

Explain these critical safety concepts essential for safe clinical practice.

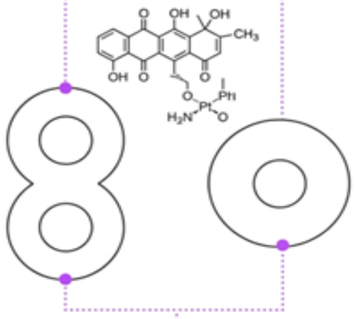
The Cell Cycle & Chemotherapy Classification

CCS (Specific)



Examples: Antimetabolites, Taxanes

CCNS (Non-Specific)



Acts: Dividing & G0 cells

Examples: Anthracyclines, Platinum analogs

Why This Distinction Matters

CCS agents *(antimetabolites, taxanes) target only actively dividing cells at specific phases — S-phase or M-phase.*

CCNS agents *(anthracyclines, platinum analogs) act on both dividing and resting G_0 phase cells, giving them greater activity against low-growth fraction solid tumors.*

The trade-off: CCNS agents also damage slow-proliferating healthy tissues, increasing systemic toxicity.

Introduction to Anthracyclines

Discovered in the 1960s from Streptomyces peucetius, anthracyclines remain among the most potent and widely used chemotherapeutics. Their bright red color earned Doxorubicin its infamous nickname: the ***"Red Devil."***

Doxorubicin
Adriamycin — most widely used

Daunorubicin
AML cornerstone

Epirubicin
Breast cancer regimens

Idarubicin
Oral AML formulations

Anthracyclines — Mechanism of Action

*Anthracyclines deploy a **three-pronged attack** on cancer cells, each mechanism reinforcing the others.*

DNA Intercalation

The drug inserts between DNA base pairs, physically blocking transcription and halting DNA/RNA synthesis.

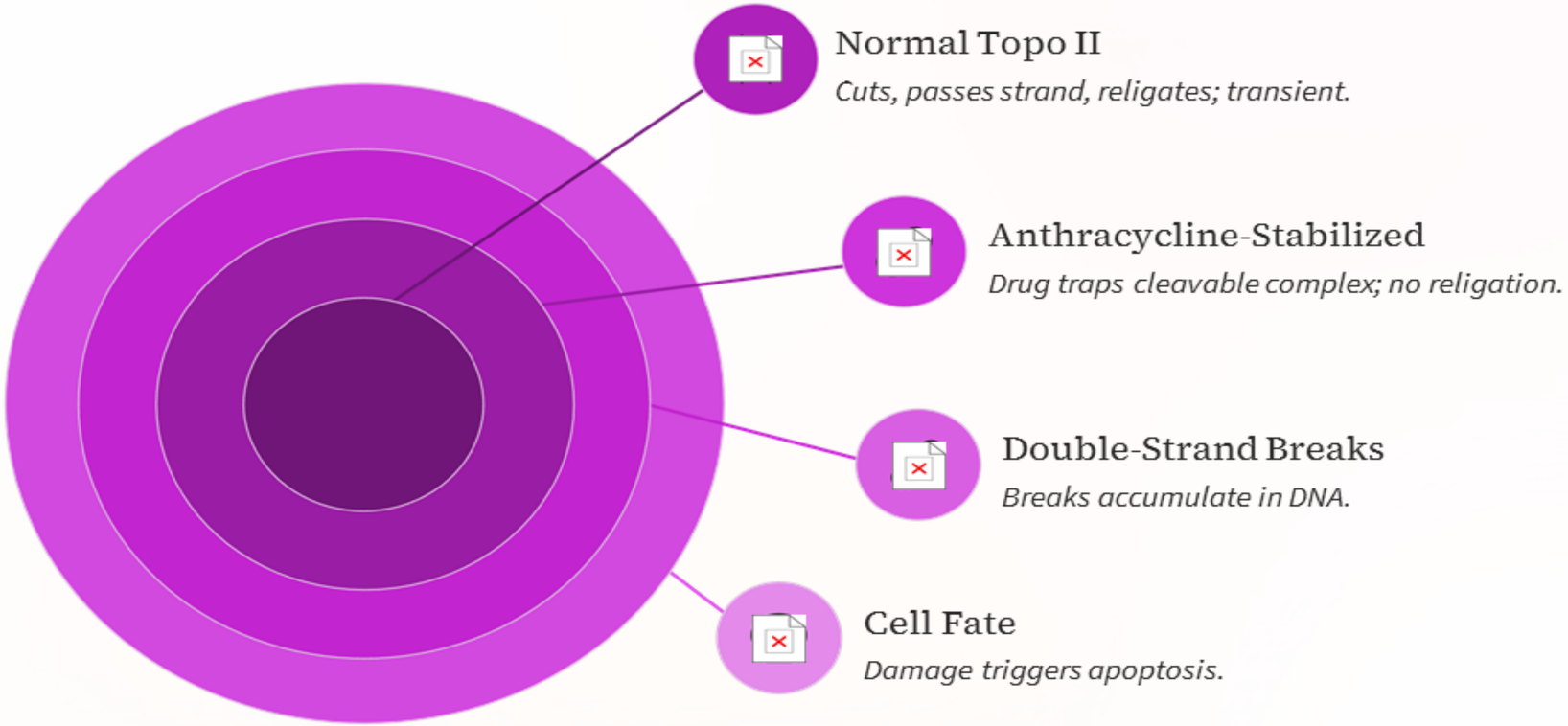
Topoisomerase II Poisoning

Stabilizes the cleavable complex, preventing DNA religation and causing lethal double-strand breaks → apoptosis.

Free Radical Generation

Produces reactive oxygen species, causing oxidative stress and membrane damage — the primary driver of cardiotoxicity.

Topoisomerase II Poisoning — The Key Mechanism



*Normally, Topoisomerase II makes transient, harmless cuts to manage DNA supercoiling. Anthracyclines **trap the cleavable complex**, preventing religation. The resulting double-strand breaks trigger apoptosis — explaining why these drugs kill even non-cycling (G_0) cells.*

Anthracyclines — Clinical Applications

Anthracyclines are backbone agents across a broad spectrum of malignancies.

Breast Cancer

AC regimen *— Adriamycin + Cyclophosphamide; a standard adjuvant and neoadjuvant backbone.*

AML

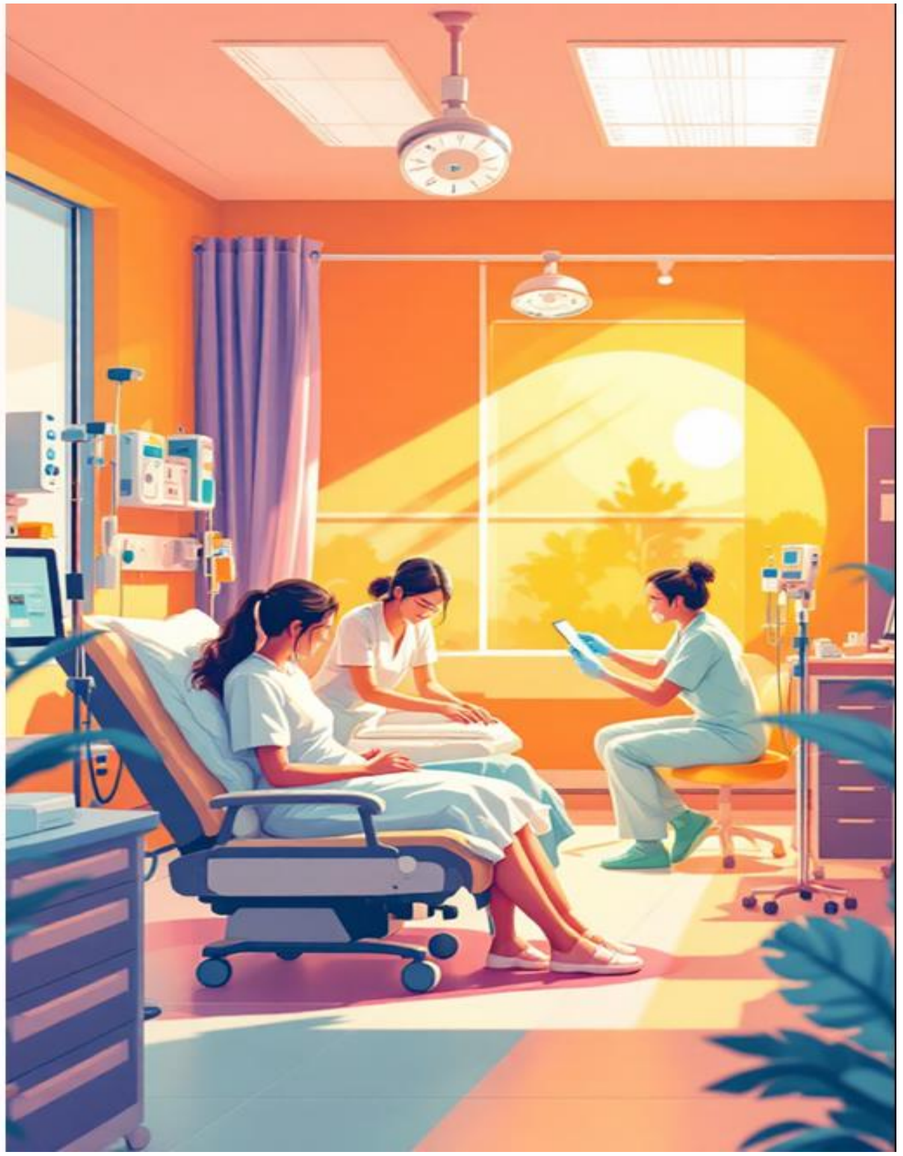
7+3 regimen *— Daunorubicin + Cytarabine; the induction standard for Acute Myeloid Leukemia.*

Lymphomas

ABVD *for Hodgkin's;* ***CHOP*** *for Non-Hodgkin's Lymphoma — both anthracycline-based.*

Sarcomas & Pediatrics

First-line for soft tissue sarcomas and many pediatric solid tumors and leukemias.



Anthracyclines — Key Toxicities

DOSE-LIMITING

Myelosuppression

Neutropenia limits the dose per cycle — the most common acute toxicity requiring growth factor support.

CUMULATIVE — MOST FEARED

Cardiotoxicity

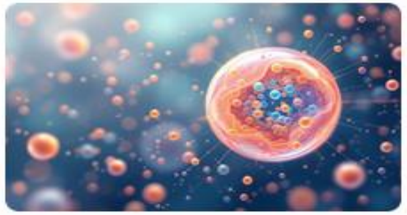
Irreversible dilated cardiomyopathy → heart failure. Risk rises exponentially with cumulative dose.

- *Doxorubicin lifetime limit:* ***450–550 mg/m²***
- *Mucositis & universal alopecia are common*
- ***Vesicant*** *— extravasation causes severe tissue necrosis*

Managing Anthracycline Cardiotoxicity

Dexrazoxane

An iron chelator that reduces free radical formation in cardiac tissue. Indicated when cumulative dose is high but therapy must continue.



Liposomal Formulations

*Doxil encapsulates doxorubicin, altering biodistribution and reducing cardiac exposure. Watch for **hand-foot syndrome** as a new toxicity.*

Monitoring Protocols

*Baseline and periodic **MUGA scans or echocardiograms** track left ventricular ejection fraction (LVEF) throughout therapy.*

Introduction to Platinum Analogs

*A serendipitous discovery — bacteria stopped dividing near platinum electrodes — led to three cornerstone agents that form **covalent DNA crosslinks**, acting as alkylating-like CCNS drugs.*

Cisplatin

Prototype agent. Highly emetogenic; nephrotoxic and ototoxic. Requires aggressive hydration.

Carboplatin

Second-generation. Dosed by Calvert formula (AUC). Myelosuppression is dose-limiting; less nephrotoxic.

Oxaliplatin

Third-generation. Colorectal cancer backbone (FOLFOX). Distinctive cumulative peripheral neuropathy.

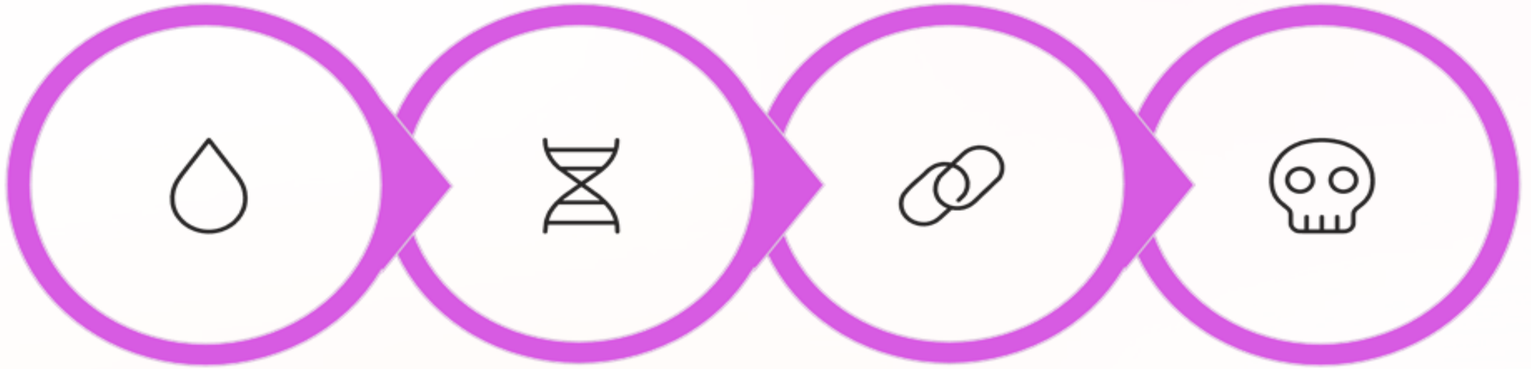
MECHANISM OF ACTION

Platinum Analogs: DNA Crosslinking

Platinum analogs kill cancer cells by covalently binding to DNA, forming crosslinks that block replication and trigger apoptosis.

MECHANISMOFACTION

How Platinums Activate and Damage DNA



The low-chloride intracellular environment is essential — it drives aquation, converting the prodrug into its active, DNA-binding form.

PHARMACOLOGY

Pharmacokinetic Differences Across Platinum Analogs

Property	Cisplatin	Carboplatin	Oxaliplatin
Dose-Limiting Toxicity	Nephrotoxicity, severe emesis, neurotoxicity	Myelosuppression (thrombocytopenia)	Neurotoxicity (acute cold-induced)
Key Indications	Testicular, bladder, head & neck	Lung, ovarian	Colorectal cancer
Dosing Method	BSA-based (mg/m^2)	Calvert Formula: Target AUC × (GFR + 25)	BSA-based (mg/m^2)
Hydration Required	Aggressive (3–4 L + mannitol)	Minimal	Minimal

CLINICAL MANAGEMENT

Toxicity Management at the Bedside

Cisplatin — Renal Protection

*Aggressive pre- and post-hydration with **3–4 L of IV fluids** plus mannitol to force diuresis and prevent nephrotoxicity.*

Carboplatin — Precision Dosing

*Apply the **Calvert Formula**: Dose = Target AUC × (GFR + 25). Individualized dosing prevents excessive myelosuppression.*

Oxaliplatin — Cold Avoidance

*Educate patients to **avoid cold drinks and surfaces**. Acute neuropathy can cause throat spasms and hand tingling on cold exposure.*

KEY CONCEPT

Dose-Limiting vs. Cumulative Toxicity

Dose-Limiting Toxicity (DLT)

Acute *— occurs days to weeks after treatment. Determines the maximum dose per cycle.*

Example: *Cisplatin → nephrotoxicity; Anthracyclines → neutropenia*

Cumulative Toxicity

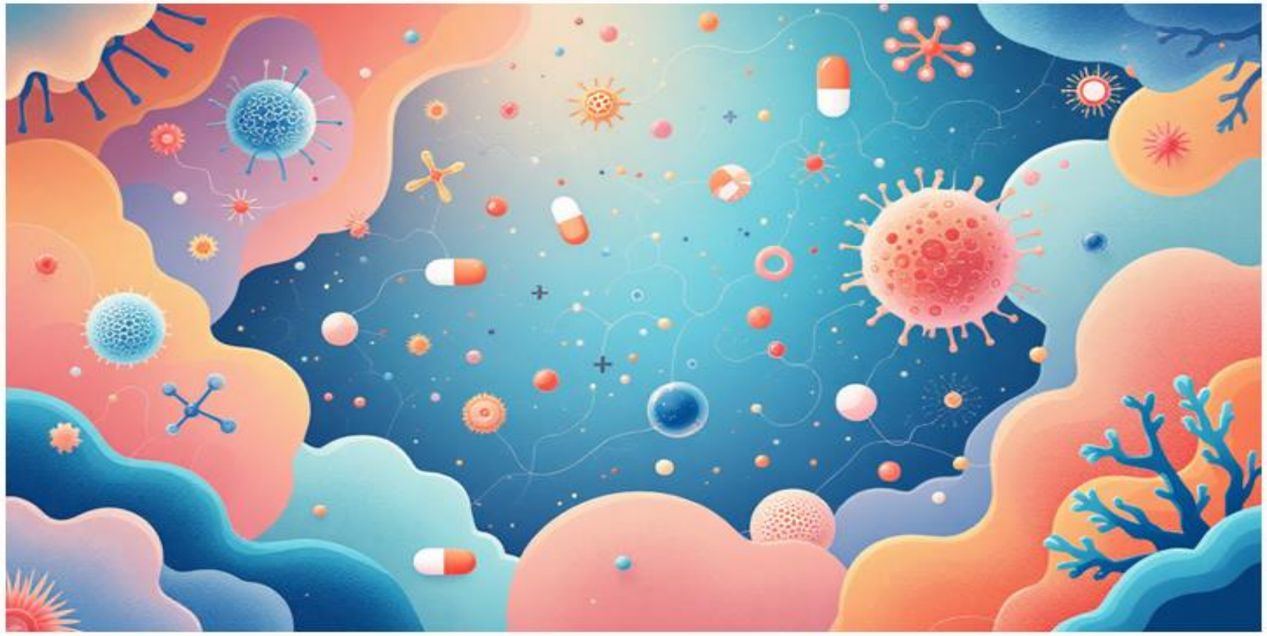
Delayed *— occurs months to years later. Determines the total lifetime cycles a patient can receive.*

Example: *Cisplatin → irreversible neuropathy; Anthracyclines → cardiomyopathy*

A patient may tolerate each cycle well yet still develop irreversible cumulative toxicity over time.

RESISTANCE

How Tumors Become Resistant



Anthracycline Resistance

*Overexpression of **MDR1 (P-glycoprotein)** — an efflux pump that actively transports doxorubicin out of the cancer cell before it can exert its cytotoxic effect.*

Platinum Resistance

*Enhanced **DNA repair pathways** (e.g., nucleotide excision repair) recognize and undo platinum-induced crosslinks before they trigger apoptosis.*

*Understanding these mechanisms drives rational **combination therapy** and the development of next-generation agents.*

CLINICAL APPLICATION

Clinical Case: 58-Year-Old with Breast Cancer

Scenario: *Starting dose-dense AC — Doxorubicin 60 mg/m² × 4 cycles + Cyclophosphamide. Normal baseline cardiac and renal function.*

01

Baseline Assessment

*Mandatory **LVEF evaluation** (MUGA or echocardiogram) before initiating therapy.*

02

Cumulative Dose Calculation

*60 mg/m² × 4 cycles = **240 mg/m²** — well within the safe lifetime limit of 450–550 mg/m².*

03

On-Treatment Monitoring

*Monitor **neutrophil count** each cycle — the dose-limiting toxicity of anthracyclines.*

04

Lifetime Dose Awareness

*Document cumulative exposure. Future anthracycline use must account for the **450–550 mg/m²** ceiling.*

REVIEW

References & Discussion Questions

Further Reading

- *Goodman & Gilman's The Pharmacological Basis of Therapeutics*
- *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*
- *NCCN and ASCO Clinical Practice Guidelines*

Review Questions

- *Why are CCNS agents effective against solid tumors with low growth fractions?*
- *What is the primary mechanism of anthracycline-induced cell death?*
- *How does carboplatin's toxicity profile differ from cisplatin's?*
- *A patient has received 500 mg/m² of doxorubicin — what monitoring is essential?*

Discussion Prompt: *How does the DLT vs. cumulative toxicity distinction change your management of a patient on cisplatin versus one on doxorubicin?*

Thank You