Part III: Anticancer Agents

Antibiotics

Classification of Antibiotics:

- Anthracycline
- Mitomycin C
- Bleomycin
- Actinomycin D
Antibiotics

Anthracyclines

• Anthracycline antibiotics are characterized by a planner oxidized anthracene nucleus fused to a cyclohexane ring that is connected by a glycosidic linkage to a amino suger.
• They are initially discovered and isolated from *Streptomyces peucetius*.

• They are DNA intercalating agents followed by inhibition of topoisomerase II resulting in strand breakage leading to apoptosis.
• These agents are primarily toxic during the S phase of cell cycle.
• **Doxorubicin** is probably the most important anticancer drug available because of its relatively broad spectrum of activity.
Doxorubicin & Daunorubicin

They:

- intercalate between base pairs
- inhibit topoisomerase II
- generate free radicals

They block RNA and DNA synthesis and cause strand scission

- **Doxorubicin** is used to treat a broad spectrum of solid tumors as well as acute leukaemias, lymphomas, and childhood tumors.
- **Daunorubicin** is indicated for acute leukaemias.
Antibiotics

Mitomycin C

• It is a natural product isolated from *Streptomyces verticillataus* as well as from other sources.

• **It act as a prodrug** activated in the body to form an alkylating agent

**Mechanism of action:**
• Mitomycin C is an antineoplastic antibiotic that **alkylates DNA** and thereby **causes strand breakage** and **inhibition of DNA synthesis**.

**Adverse Effects:**
• Mitomycin produces prolonged **myelosuppression** that preferentially affects platelets and leukocytes.
Antibiotics

Actinomycin D

- The actinomycins are a class of **polypeptide antibiotics** isolated from **soil bacteria** of the genus **Streptomyces**, of which the most significant is actinomycin D.

- Actinomycin D **intercalates** DNA and thereby **prevents** DNA transcription and messenger RNA synthesis.

- The drug is given **intravenously**, and its clinical use is limited to the treatment of **trophoblastic (gestational) tumors** and the treatment of **pediatric tumors**.
Bleomycin

- Bleomycins were first discovered in 1966.
- Bleomycin is a mixture of **Bleomycin A2 and B2** isolated from *Streptomyces verticillus*. It is used by IV/IM in combination therapy for treatment of certain types of skin cancer, and testicular carcinoma.
Antibiotics

Bleomycin

**Mechanism of Action:**
- The drug has its greatest effect on neoplastic cell in the **G2 phase** of the cell replication cycle.
- Bleomycin intercalates DNA, and acts through binding to DNA, which results in single and double strand breaks following free radical formation and inhibition of DNA synthesis.
- The DNA fragmentation is due to oxidation of a DNA-bleomycin-Fe(II) complex and leads to chromosomal aberrations

**Clinical indication:** carcinoma of cervix, head and neck, larynx, penis, skin, testes, Hodgkin’s and non-Hodgkin’s lymphoma.

**Adverse Effects:** Myelosuppression, Pneumonitis/pulmonary fibrosis
Part IV
Anti-Cancer Plant Alkaloids

Plant Alkaloids

Vinca Alkaloids
  Vinicristine
  Vinblastine

Taxanes
  Paclitaxel
  Docetaxel

Podophyllotoxins
  Etoposide
  Teniposide

Camptothecins
  Topotecan
  Irinotecan
Mitotic inhibitors

- Mitotic inhibitors are often plant alkaloids and other compounds derived from natural products. They can stop mitosis or inhibit enzymes from making proteins needed for cell reproduction.

Paclitaxel

Vincristine
Tubulin-Binding Agents

Vinca Alkaloids: Vinicristine and vinblastine

• These are obtained from Catharanthus roseus (Vinca rosea).
• They are dimeric indole-dihydroindole derivatives.
• These drugs block the formation of mitotic spindle/filaments for nuclear and cell division by preventing the assembly of tubulin dimers into microtubules.

\[
\begin{align*}
\text{Vinblastine} & \quad R = \text{CH}_3 \\
\text{Vinicristine} & \quad R = \text{CHO}
\end{align*}
\]
Vinka alkaloids

α-tubulin  β-tubulin  α and β tubulin heterodimers

Section of a Microtubule

α and β tubulin heterodimers
Vincristine sulfate (Oncovin®)

Uses:
• leukemias, lymphomas, sarcomas, and some carcinomas

Vinblastine sulfate (Velban®)

Uses:
• Vinblastine, the **more active compound**, has had much wide clinical application, including solid tumors, especially in combination with drugs such as cisplatin and BLM (bleomycin)
• testicular tumor
• advanced Hodgkin’s disease
• breast carcinoma
Anti-Cancer Plant Alkaloids

Mitotic Inhibitors (Tubulin-Binding Agents)

Paclitaxel (Taxol) and Docetaxel

- **Paclitaxel** and the **semisynthetic analogue Docetaxel** represent the taxane family of drugs that **inhibit tubulin depolymerisation**.
- Paclitaxel was isolated from the bark of Yew trees *Taxus brevifolia* in **1962**.
- A full synthesis was achieved in **1994**.
- The **semisynthetic route involves docetaxel as an intermediate**.
- The term **Taxoids** is used generally for paclitaxel and its derivatives.
- **MAO**: The taxoids binds to β-subunit of tubulin and accelerates polymerisation as well as stabilises the resultant microtubules, which means that depolymerisation is inhibited. As a result, the cell division cycle is halted.
Vinka alkaloids

Indirect

Direct

\[\text{Paclitaxel (Taxol)}\]

\[\text{Stabilise}\]

\[\text{\(\alpha\) and \(\beta\) tubulin heterodimers}\]

\[\text{\(\alpha\)-tubulin} \quad \text{\(\beta\)-tubulin}\]
Paclitaxel (Taxol)

**Uses**
- Leukemias, sarcomas,
- lung cancer
- ovarian and breast carcinoma

**Side effects:** hair loss, muscle and joint pains, and diarrhea

Docetaxel

**Uses**
- lung cancer
- ovarian and breast carcinoma
Podophyllum

- Podophyllum resin is obtained from rhizomes or roots of *Podophyllum peltatum* (American podophyllum) or *Podophyllum emodi* (Indian podophyllum). Family: Berberidaceae.
- It is known as May apple.

Constituents:
- It contains 3.5 - 6% of resin.
- The active principle is the lignans, these include podophyllotoxin 20%, α-peltatin 10%, and β-Peltatin 5%.
- Etoposide is a lignan derivative obtained semi-synthetically from podophyllotoxin and is used for treatment of small-cell lung cancer, testicular cancer as well as lymphomas and leukemias.
- Teniposide (synthetic derivative of podophyllotoxin) is also used for the treatment of brain cancer.
Campetothecine

- It is obtained from the Chinese tree *Camptotheca acuminata*, and family *Nyssaceae*.
- This alkaloid showed broad spectrum activity as **anticancer** but its toxicity is too high.
- The natural **10-hydroxy camptothecin** is more active and is used in China for **neck** and **head cancer**.
- The synthetic analogues are 9-aminocamptothecin.
- Particularly, water-soluble derivatives **topotecan, irinotecan** showed good for the treatment of **ovarian cancer** and **colorectal cancer**, while **belotecan** (camtobell ® available in USA) is available for small cell **lung cancer** and **ovarian cancer**.
- **Irinotecan inhibits the action of topoisomerase I** by binding to topoisomerase I-DNA complex, and causes double-strand DNA breakage and cell death.
- **Side effect of irinotecan**: diarrhea, anemia, hair loss, abdominal
Irinotecan

Camptothecine

Topotecan

Camptotheca acuminata
Topoisomerase inhibitors

• Interfere with enzymes called topoisomerases, which help separate the strands of DNA so they can be copied

[Chemical structures of Topotecan and Etoposide]

Topotecan
(tooisomerase I inhibitor)

Etoposide
(tooisomerase II inhibitor)
Topoisomerase I and II (Video Presentation)

https://www.youtube.com/watch?v=EYGrElVyHnU

Topoisomerase solves

A KNOTTY PROBLEM
Hormone therapy

- Drugs in this category are sex hormones, or hormone-like drugs, that change the action or production of female or male hormones.

- They are used to slow the growth of breast, prostate, and endometrial (uterine) cancers, which normally grow in response to natural hormones in the body.

- These cancer treatment hormones do not work in the same ways as standard chemotherapy drugs, but rather by preventing the cancer cell from using the hormone it needs to grow, or by preventing the body from making the hormones.

![Tamoxifen](image1.png)  ![Exemestane](image2.png)  ![Estrone](image3.png)
Common Chemotherapy Side Effects

• Although chemotherapy is given to kill cancer cells, it also damages normal cells.

• The normal cells most likely to be damaged are those that divide rapidly, for instance:
  – Bone marrow/blood cells
  – Cells of hair follicles
  – Cells lining the digestive tract
  – Cells lining the reproductive tract

• Common side effects
  – Hair loss
  – Anemia
  – Infertility
  – Infections
  – Nausea and Vomiting
  – Peripheral Neuropathy
  – Second Cancers Caused by Cancer Treatment
Combination of chemotherapy with other treatments

• Adjuvant chemotherapy
After surgery to remove the cancer, there may still be some cancer cells left behind that cannot be seen. When drugs are used to kill those unseen cancer cells, it’s called adjuvant chemotherapy. Adjuvant treatment can also be given after radiation. An example of this would be adjuvant hormone therapy after radiation for prostate cancer.

• Neoadjuvant chemotherapy
Chemotherapy can be given before the main cancer treatment (such as surgery or radiation). Giving chemotherapy first can shrink a large cancerous tumor, making it easier to remove with surgery. Shrinking the tumor may also allow it to be treated more easily with radiation. Neoadjuvant chemotherapy also can kill small deposits of cancer cells that cannot be seen on scans or x-rays.
Other types of chemotherapy drugs

• **Targeted therapies** - e.g. imatinib (Gleevec®), gefitinib (Iressa®),
  - Attack cancer cells more specifically than traditional chemotherapy drugs
  - Most attack cells with mutant versions of certain genes, or cells that express too many copies of a particular gene

• **Differentiating agents** – e.g. retinoids, tretinoin (ATRA or Atralin®)
  - Make cancer cell mature into normal cells

• **Immunotherapy** – e.g. rituximab (Rituxan®), cancer vaccines
  - Stimulate natural immune systems to recognize and attack cancer cells
  - **Active immunotherapies** stimulate the body’s own immune system to fight the disease
  - **Passive immunotherapies** do not rely on the body to attack the disease; instead, they use immune system components (such as antibodies) created outside the body.
What is targeted therapy?

- Cytotoxic chemotherapy preferentially selects for rapidly dividing cells, which means that it affects both highly proliferative normal tissues (e.g., hair, the linings of the gastrointestinal tract, bone marrow) and malignant cells.

- **Targeted therapy**
  - Medication or drug that targets a specific pathway in the growth and development of a tumor cell.
  - The targets themselves are typically various molecules (or small particles) in the body that are known or suspected to play a role in cancer formation.
  - Monoclonal antibodies or small molecule inhibitors directed against molecules that are either overexpressed or mutated in cancerous cells.
  - Many of these targets are tyrosine kinases, which are enzymes found within cells that transfer phosphate groups and affect molecular signaling.
Epidermal Growth Factor Receptor (EGFR)

- EGFR exists on the cell surface and is activated by binding of its specific ligands.
- Upon activation by its growth factor ligands, EGFR undergoes a transition from an inactive monomeric form to an active homodimer.
- EGFR dimerization stimulates its intrinsic intracellular protein-tyrosine kinase activity.
- As a result, autophosphorylation of several tyrosine (Y) residues in the C-terminal domain of EGFR occurs.
- This autophosphorylation elicits downstream activation and signaling leading to DNA synthesis and cell proliferation.
- Mutations that lead to EGFR overexpression or overactivity have been associated with a number of cancers, including lung cancer.
Gefitinib (IRESSA®)

- Gefitinib targets the EGFR family of receptors mainly in **lung cancer**.

- **Inhibits EGFR tyrosine kinase** by binding to the adenosine triphosphate (ATP)-binding site of the enzyme.

- Thus the function of the EGFR tyrosine kinase transduction cascade is inhibited, and malignant cells are inhibited.
HER2 and cancer

- Amplification or over-expression of the HER2 gene occurs in approximately 15-30% of breast cancers.
- It is strongly associated with increased disease recurrence and a poor prognosis.
Trastuzumab (Herceptin)

It is a monoclonal antibody that interferes with the HER2/neu receptor.