General Principles of Chemotherapy- An Introduction to Mechanism of Cytotoxic Drugs

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Effects of various treatments on the cancer cell burden in a hypothetical patient
Objectives

- Describe several categories of chemotherapy drugs.
- Describe the therapeutic action of the various chemotherapy drugs.
- Describe the cell cycle in relation to the mode of action of the chemotherapy drugs.
- Describe the toxicities that are common to the class and the toxicities that are unique to specific drugs within that class.

Mechanism of Action

- As a generalization, cytotoxic drugs can be described as anti-proliferative, with DNA the end target.
- The activity may be by direct attack on DNA, or indirectly through disruption of the essential process in the formation, function, or maintenance of DNA.
**Action sites of cytotoxic agents**

- DNA synthesis: Anti-metabolites
- DNA transcription: Intercalating agents
- DNA duplication: Mitosis
- Cellular level: DNA
- Spindle poisons: Intercalating agents
- Cell cycle and cytotoxic opportunities: G1 Period
- Cell division: S-phase (Chromosome replication)
- Life cycle: G2 Period
- Cell differentiation
- Time: Cell life cycle
**Action sites of cytotoxic agents**

**Cell cycle level**

- **Antibiotics**
- **Antimetabolites**
- **Alkylating agents**
- **Vinca alkaloids**
- **Mitotic inhibitors**
- **Taxoids**

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**The cell cycle and cytotoxic drug action - relevance to clinical use**

- Cell Cycle **Phase** Specific - drugs that are effective only when cells are in a particular phase of the cell cycle.

- The broader term Cell Cycle Specific (CCS) refers to agents with activity at any non-resting phase.

(e.g. Antimetabolites - Methotrexate & Fluorouracil)
The cell cycle and cytotoxic drug action - relevance to clinical use

- Cell Cycle Phase Non-Specific- drugs that act regardless of where cells are in the cell cycle. (e.g. Cyclophosphamide, Doxorubicin)
- Active in many phases, and consequently are not schedule dependent.
- The activity of this group of drugs depends on the dose- Dose dependent.

Dose response curve for cytotoxic drugs

- Dose response curve is steep for most cytotoxic drugs.
  - Difference between therapeutic effect and toxicity may not be great.
  - Small reductions may substantially reduce effect.
  - ↓Dose may reduce cure rate while not reducing response rate.
Dose response curves - steep for most cytotoxic drugs

Pharmacology of individual agents

- Focus on mechanisms and functions considered important.
- Cytotoxic drugs can be classified according to the mode of action or chemical class.
- Drugs in a same class may show similar properties (i.e. taxanes, anthracyclines) or include agents with very different properties (antitumour antibiotics)
Chemical Classification

<table>
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<tr>
<th>Alkylating Agents</th>
<th>Anti-Metabolites</th>
<th>Antibiotics</th>
<th>Camptothecans</th>
<th>Mitotic Inhibitors</th>
<th>Epiphyllotoxins</th>
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<tr>
<td>Busulphan</td>
<td>Capecitabine</td>
<td>Bleomycin</td>
<td>Irinotecan</td>
<td>Docetaxel</td>
<td>Etoposide</td>
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<tr>
<td>Carmustine</td>
<td>Cytosine</td>
<td>Dactinomycin</td>
<td>Topotecan</td>
<td>Paclitaxel</td>
<td>Teniposide</td>
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<tr>
<td>Chorambucil</td>
<td>Arabinose</td>
<td>Daunorubicin</td>
<td>Vinblastine</td>
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<tr>
<td>Cisplatin</td>
<td>Mercaptopurine</td>
<td>Doxorubicin</td>
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<td>Vincristine</td>
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<tr>
<td>Cyclophosphamide</td>
<td>Methotrexate</td>
<td>Mitomycin-C</td>
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<td>Vindesine</td>
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<tr>
<td>Ifosfamide</td>
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<td>Mitoxantrone</td>
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Alkylating Agents

- First clinically used cytotoxic drugs.
- Diverse group of chemically reactive agents.
- Have the same general mode of action.
  - Bonding to the DNA
- However, from a therapeutic point of view, they have differences that make them quite diverse.
Cyclophosphamide induced cystitis

- Damage to the bladder epithelium and haemorrhagic cystitis is a side effect unique to cyclophosphamide and ifosfamide.
- Acrolein generated from 4-hydroxy cyclophosphamide is responsible for the urological toxicity.
- Symptoms range from mild irritative voiding to severe life threatening haemorrhagic cystitis.
- Adequate hydration is used to prevent bladder toxicity.
Cyclophosphamide induced cystitis

- The uroprotectant mesna is used when large doses of cyclophosphamide are used or when patients have evidence of bladder toxicity from previous treatment.
- In the blood stream mesna is very rapidly converted to the inactive dimesna from. It is not considered to interfere with the cytotoxic properties of cyclophosphamide.
- In the kidney dimesna converts back to mesna before accumulating in the bladder where it serves as a surrogate target for acrolein.
- Mesna has short half life of 1.5 hours means that administration is critical.

Ifosfamide

- Ifosfamide is an analogue of cyclophosphamide with arguable clinical advantages.
- Metabolism and end mechanism of action is similar.
- There are however, distinct differences in toxicity.
  - Bladder toxicities is much greater with ifosfamide.
  - Risk of debilitating reversible neurotoxicity.
Platinum analogues

- Action similar to conventional alkylating agents.
- Cisplatin and Carboplatin have two reactive sites each and can effectively cross link DNA.
- Platinum analogues have become an extremely important part in the curative treatment for solid malignancies.
- Carboplatin modified ring structure reduced its chemical reactivity but improved its side effect profile compared to cisplatin.

Clinical differences

<table>
<thead>
<tr>
<th></th>
<th>Cisplatin</th>
<th>Carboplatin</th>
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</thead>
<tbody>
<tr>
<td><strong>Myelosuppression</strong></td>
<td>✓</td>
<td>✓ ✓</td>
</tr>
<tr>
<td><strong>Nephrotoxicity</strong></td>
<td>✓ ✓</td>
<td>x</td>
</tr>
<tr>
<td><strong>Hypomagnesaemia</strong></td>
<td>✓</td>
<td>x</td>
</tr>
<tr>
<td><strong>Hyper hydration</strong></td>
<td>✓</td>
<td>x</td>
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<tr>
<td><strong>Otototoxic</strong></td>
<td>✓</td>
<td>x</td>
</tr>
<tr>
<td><strong>Neuropathy</strong></td>
<td>✓</td>
<td>x</td>
</tr>
<tr>
<td><strong>Emetogenicity</strong></td>
<td>✓ ✓ ✓</td>
<td>✓</td>
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Oxaliplatin

- 3rd generation platinum derivative.
- Forms bulky DNA adducts and induces cellular apoptosis.
- Synergy with 5-FU. Down regulation of thymidylate synthase by Oxaliplatin.
- Toxicity profile differs from those of carboplatin and cisplatin.

Oxaliplatin

- Renal dysfunction, alopecia and ototoxic effects are uncommon.
- Neuropathy is more frequent-
  - Transient dysesthesias, manifested as numbness or tingling of the hands and feet and the oral or perioral regions, which are exacerbated by exposure to low temperature.
  - Cumulative dose-dependant sensory neuropathy in which peripheral dysesthesias and parathesias persist between cycles of therapy.
Anti-tumour antibiotics

- Diverse group of drugs originating from bacterial culture- *Streptomyces*.
- Considerable more toxic to mammalian cells than bacteria.
- The structures, mechanism of action, toxicities and clinical usefulness varies enormously.

Anthracyclines

- Characterised by their red colour and their unique chemical structure.
- All have four ringed planar structure with a sugar moiety attached.
- Doxorubicin, Daunorubicin, Epirubicin and Idarubicin
Anthracylines-mode of action

- Were originally considered to "intercalate" DNA.
- Two major mechanism of action:
  - Inhibition of Topoisomerase II
  - Generation of free radicals.

Topoisomerase II inhibitors prevent the rejoining of DNA

1. Topoisomerase II inhibitor attaches to topo-II / DNA complex.
2. DNA strands are broken but rejoining does not occur.
3. DNA strand breaks result. Number of strand breaks correlates with cell death.
Generation of free radicals

- Antracylines participate in chemical redox reactions and hence are capable of propagating free radical formation.
- Free radicals are highly destructive, and can cause considerable damage to DNA.
- Mechanism of anthracycline induced cardio toxicity.

Anthracycline induced cardiomyopathy

- All anthracyclines are capable of producing an irreversible cardiomyopathy.
- Factors include the following
  - Total cumulative dose
  - Method or schedule of administration
  - Concurrent therapy
  - Pre existing heart disease
  - Previous use of other anthracyclines
Total dose limits for anthracyclines

- Total lifetime cumulative dose is:-
  - Doxorubicin 400-450mg/m²
  - Daunorubicin 450-550mg/m²
  - Epirubicin 900-1000mg/m²
  - Idarubicin 150mg/m²

- Based on bolus administration.
- No pre-existing cardio toxicity, hepatic impairment, previous medastinal radiotherapy or high dose cyclophosphamide.
Anthracenediones-mitozantrone

- Closely related to anthracyclines and spectrum of activity similar to anthracyclines.
- Some differences in mechanism and toxicity.
  - Less reactive than anthracylines.
  - Much reduced level of cardio toxicity.
  - Extravasations is unlikely to cause ulceration.
- ‘Mild’ alternative to anthracylines.

Bleomycin

- Belomycin is notable cytotoxic drug.
- It lacks haematological toxicity, which is unusual.
- A mixture of 13 complex glycoproteins derived from the fermentation of *streptomyces verticullis*.
- Cell cycle specific, having greatest effect on cells in the S and G₂ phase.
- It acts by combining with Fe⁺⁺ to form a reactive complex, which associates strongly with DNA and is able to generate O₂ free radicals.
- Type I hypersensitivity can occur (fevers and chills).
Bleomycin Lung Toxicity

- It has a unique and serious lung toxicity
  - Lung and skin tissues are relatively low in the enzyme bleomycin hydrolase.
- Lifetime cumulative dose of 300 IU
  - Lung irradiation
  - Concurrent use of high oxygen conc, and
  - Renal impairment increases the risk.
- Skin Toxicity is marked by bullous reactions over palms or hands.

Relationship between total cumulative dose of bleomycin and lung toxicity

- < 500 IU incidence 8-12%
- > 500 IU incidence 30%
ANTIMETABOLITES

- Diverse group of drugs that act by mimicking the natural substrates and enzymes critical in the formation, function and maintenance of DNA.
- Act as a false or faulty substrate and generally can be described as causing competitive inhibition.

Antimetabolites

- Cell Cycle Specific- act only on cells in the ‘S’ phase of the cell cycle.
- There is a threshold to activity, i.e. that is conc. below which they have no action.
- Cytotoxic effects of antimetabolites are increased when there is continued exposure above a certain threshold.
Folate antagonists
(methotrexate & premetrexed)

- MTX acts as a mimic of folic acid.
- Inhibits the conversion of folic acid to tetrahydrofolate by competitively inhibiting the mammalian dihydrofolate reductase.
- Results in the inhibition of DNA synthesis via blockage of thymidine and purine synthesis.
- Premetrexed is a multitargeted antifolate.
- Has wide clinical spectrum of activity.

Methotrexate

- Vigorous hydration and alkylation of the urine is necessary to decrease risk of kidney damage.
- Drugs that are highly protein bound may increase the toxicity of MTX due to displacement from Albumin of MTX (phenytoin, salicylates, sulfonamides)
- High dose therapy is lethal and require leucovorin rescue
- Calcium folinate ‘antidote’ is used 20-42 hrs after high dose to effectively ‘turn off’ further methotrexate activity.
Leucovorin administration when MTX levels are ≥ 1µM at 48 hours

- Dose is 15mg/m² and titrated according to the MTX conc. (stop at conc. of 0.1 µM)

<table>
<thead>
<tr>
<th>MTX level</th>
<th>Leucovorin dose for the next 24 hours</th>
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</thead>
<tbody>
<tr>
<td>1-5 µM</td>
<td>50mg/m² IV Q6H</td>
</tr>
<tr>
<td>5.01-10.0 µM</td>
<td>100mg/m² IV Q6H</td>
</tr>
<tr>
<td>10.1-20.0 µM</td>
<td>200mg/m² IV Q6H</td>
</tr>
</tbody>
</table>

Pyrimidine Analogonist-5-FU

- Mimic of uracil, the natural substrate for DNA and RNA synthesis.
- Act primarily by inhibiting thymidylate synthase, the rate limiting enzyme in pyrimidine nucleotide synthesis.
- Requires intracellular activation to exert cytotoxic effect i.e. 5-FU is a pro-drug.
- Co-treatment with Folinic Acid stabilises the ternary complex of FdUMP and Thymidylate Synthetase and greatly enhances the activity of 5-FU by enhancing the inhibition of DNA synthesis.
5-Fluorouracil

- Major side effects associated with 5-FU depend on method of administration:
  - Bolus Loading treatment- Neutropenia and Stomatitis.
  - Weekly bolus- Diarrhoea more frequent.
  - Continuous infusion- Less haematological and gastrointestinal but palmar-plantar Erythemia (‘Hand-foot syndrome’).

Purine analogues

- These mimic deoxyadenosine, catabolised along the same pathway as deoxyadenosine but either resist removal by deoxyadenosine deaminase (e.g. fludarabine and cladrabine) or inactivate it (pentostatin).
- Activity limited to CLL and hairy cell leukaemia.
- Myelosuppression due to T cell depletion and requires prophylactic antibiotics.
- Other purine analogues include Thioguanaine and Mercaptopurine.
Pyrimidine analogues
Cytosine Arabinoside

- Mimics natural pyrimidine (cytidine) and competitively inhibits DNA polymerase.
- Incorporates into DNA chains as a faulty component.
- Short half-life and is highly specific for the “S” phase of the cell cycle.
- Rash and drug fever are not uncommon
- Cerebella toxicity, pulmonary distress, and transient conjunctivitis seen with high doses.

Gemcitabine

- Clinically very different to Ara-C
- Cytarabine is restricted to the treatment of haematological malignancies.
- Gemcitabine has considerable activity against NSCL, Bladder, GI.
- Therapeutic and toxicological effects of gemcitabine are remarkably dependent on administration schedules used.
Epidophyllotoxins (Etoposide and Teniposide)

- Semisynthetic derivative of podophyllotoxin.
- Cell cycle specific agents that cause cell death by inhibiting topoisomerase II.
- IV infusion should be over 30-60mins to avoid hypotension.
- IV solution should be diluted to a conc. <0.4mg/ml.
- Oral absorption is 50% when compared to IV.
- Causes classical myleosuppression.
- Hypersensitivity reactions (i.e. BP changes and can occur in some patients.

Mitotic spindle poisons

- Vinca alkaloids (vincristine, vinblastine, vinorelbine) and taxanes (paclitaxel and docetaxel).
- Affect cells in mitosis by inhibiting either the formation (vinca alkaloids) or the disassembly (taxanes) of microtubules.
- Cell cycle specific for the M phase.
**Mitosis**

![Mitosis Image](image)

**Vinca alkaloids**

- Metabolism predominantly hepatic.
- All cause neurotoxicity- proportional to dose and dose intensity of administration.
  - Peripheral neuropathy- effects tends to be additive especially if weekly administration
    - Numbness, tingling and pain in a glove-sock distribution.
  - Autonomic- tends to occur 3-5 days after a dose
    - Effects more pronounced in elderly and liver impairment.
    - Prophylactic laxatives app for most patients or dose red.
**Taxanes**

- Inhibit Microtubular disassembly and cell cycle phase specific for the M Phase.
- Two currently available drugs are paclitaxel and docetaxel.
- Clinical differences between the two.

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**Paclitaxel**

- Paclitaxel is phase specific.
- Established indications: Ovarian & Breast Hypersensitivity reactions. pre-medication is mandatory.
- Sensory peripheral neuropathy is dose limiting.
- Parathesia is common and distribution follows a glove/stocking distribution.
Docetaxel

- Schedule independent anticancer effect.
- Established indications; Lung, Prostate, Breast
- Non-cardiac, non-renal oedema which appears to be the result of capillary damage.
- Effects are cumulative with repeated cycles.
- Prophylactic use of dexamethasone.

Sequence of cytotoxic drug administration

- Order of adm. of cytotoxic drugs can have significant effect on therapeutic outcome and toxicity.
- Methotrexate-cisplatin: Delayed methotrexate renal clearance if given after cisplatin.
- Paclitaxel-cisplatin: Clearance of paclitaxel decreased if given after cisplatin
- Fomustine-DTIC: combination of both drugs results in incidence of lung fibrosis not associated if the drugs are given separately.
Conclusions

- Understanding of the mechanism of action of major class of cytotoxic drugs helps in the understanding of the side effects of chemotherapy and more importantly how to predict and manage these side effects.