Principles of chemotherapy
Chemotherapy first coined by Paul Ehrlich
Aim to selectively destroy cancer cells whilst relatively sparing tumours cells
Growth characteristics of cancer cells allows for selective killing
Growth fraction highest when tumours small (calculated to be 37% of maximal size). Explains why chemotherapy generally more effective when tumour burden low
Types of cytotoxic drugs (6)
Alkylation agents
- Cyclophosphamide
- Cisplatin
Antitumour metabolites
- Gemcitabine
- Methotrexate
- 5 FU
- Mercaptopurine
- Thiouracil
Antitumour antibiotics
- Doxorubicin/epirubicin
- Mitomycin C
- Bleomycin
Plant derived agents
- Vincristine & vinblastine
- Docetaxel & Paclitaxel
- Etoposide
Biological agents
- BCG
- Interferon
- Tyrosine kinase inhibitors
  - Bevacizumab
Hormonal agents
- Tamoxifen
- Oestrogens

<table>
<thead>
<tr>
<th>Class</th>
<th>Example</th>
<th>Mode of action</th>
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<tbody>
<tr>
<td>Antimetabolites</td>
<td>Antifolates, MTX, 5FU</td>
<td>Inhibit steps in one carbon metabolism for purine synthesis – MTX inhibits dihydrofolate reductase, 5FU inhibits thymidylate synthetase</td>
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<td>Purine analogs: 6-mercaptopurine</td>
<td>Inhibit de-novo purine synthesis</td>
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<tr>
<td>Antibiotics</td>
<td>Bleomycin</td>
<td>Causes breaks in DNA</td>
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<tr>
<td></td>
<td>Doxorubicin</td>
<td>Interferes with topoisomerase II and causes DNA breaks</td>
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<tr>
<td></td>
<td>Mitomycin C</td>
<td>Crosslinks DNA</td>
</tr>
<tr>
<td>Platinum analogs</td>
<td>Cisplatin</td>
<td>Binds to DNA and forms DNA adducts</td>
</tr>
<tr>
<td>Alkylation agents</td>
<td>Melphalan, chlorambucil, cyclophosphamide</td>
<td>Binds to DNA and forms DNA adducts</td>
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<tr>
<td>Vinca alkaloids</td>
<td>Vinorelbine, vincristine</td>
<td>Binds to tubulin causing mitotic arrest</td>
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<tr>
<td></td>
<td>Paclitaxel</td>
<td>Binds to microtubules</td>
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<td></td>
<td>Etoposide</td>
<td>Interferes with topoisomerase II and inhibits nucleoside transport</td>
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<tr>
<td>Topoisomerase inhibitors</td>
<td>Camptothecin</td>
<td>Inhibits topoisomerase I and unraveling of DNA before replication fork</td>
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<tr>
<td>Acridine dyes</td>
<td>Amscarine</td>
<td>Intercalates DNA causing DNA breaks</td>
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<tr>
<td>Retinoids</td>
<td>Retinol</td>
<td>Causes differentiation of malignant cell</td>
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</tbody>
</table>
The cell cycle

Cell Cycle

Kinetic classification of chemotherapeutic agents

(i) Phase-specific

S-phase
- Gemcitabine
- Hydroxyurea
- Thiouracil/Fluorouracil
- Methotrexate
- Mercaptopurine

M-phase
- Vincristine/vinblastine
- Docetaxel/paclitaxel

(ii) Cell-cycle non-specific

Alkylating agents
- Mitomycin C
- Cisplatin
- Carboplatin
- Cyclophosphamide

Topoisomerase II
- Doxorubicin
- Etoposide

(iii) Cell-cycle independent

Bleomycin
Nitrosureas

Pharmacotherapy
Dosed vs. g/mg per square metre surface area
Maximum dose limited by:
- Toxic effects on rapidly dividing normal cells (bone marrow/intestine)
- Renal and liver function
- Hepatic function important for epirubicin, mitoxantrone, methotrexate, vinca alkaloids. Renal function important for cisplatin, methotrexate etc.
<table>
<thead>
<tr>
<th>Selected complications</th>
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</thead>
<tbody>
<tr>
<td>Tissue destruction</td>
<td>Vinca alkaloids, doxorubicin</td>
</tr>
<tr>
<td>Bone marrow toxicity</td>
<td>All agents</td>
</tr>
<tr>
<td>N &amp; V (CTZ)</td>
<td>Cisplatin, cyclophosphamide, doxorubicin</td>
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<tr>
<td>Mucositis</td>
<td>Methotrexate</td>
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<tr>
<td>Diarrhoea</td>
<td>5 FU and cyclophosphamide</td>
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<td>Hair loss</td>
<td>Doxorubicin, cyclophosphamide, etoposide, vincristine and paclitaxel</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>All alkylating agents. Usually leukaemia – new solid tumours very rare</td>
</tr>
<tr>
<td>Infertility</td>
<td>Usually alkylating agents</td>
</tr>
</tbody>
</table>
Appendix

G1

**Gap 1**

Preparation for DNA synthesis

G1-S checkpoint

Cell cycle progression mediated by interaction of cyclins and cyclin-dependent kinases

Intracellular and extracellular signals such as DNA damage and hypoxia activate cdk inhibitors (p16, p19, p21) which ‘brake’ cycling

**p53 crucial control protein**

- Activated by DNA damage and hypoxia (phosphorylation) - dissociates from MDM2 protooncogene
- Stimulates genes responsible for cell-cycle arrest, DNA repair and apoptosis
- Rb usually binds to E2F preventing final common pathway. Cyclin –CDK complexes phosphorylate Rb allowing free E2F to stimulate cycling

**DNA synthesis**

- Purines = adenine and guanosine
- Pyrimidines = cytosine, thymidine
- Cytosine forms hydrogen bonds with guanosine
ChemoRx and RadioRx

Adenine forms hydrogen bonds with thymidine
DNA polymerase
DNA sensing performed by ATM kinase – allows for
continued surveillance for DNA abnormalities

G2
Gap 2
Preparation for mitosis
G2-M checkpoint
Unlike G1-S, only responds to DNA damage – ATM
therefore important in mediating radiation induced
damage
cyclin B-cdc2 and cyclin A-cdc2 most important cyclins –
activate spindle assembly and chromatin unfolding
proteins

KEY POINTS: THE CELL CYCLE

The cell cycle allows the ordered replication of each cell into two daughter cells.
Primary points of cell cycle controls are G1, S, and G2/M.
Expression of TP53 results in cell cycle arrest and repair of DNA damage. If the DNA damage cannot be repaired, TP53 stimulates cell death (apoptosis)
TP53 is the most commonly mutated gene in cancer and plays a prominent role in genitourinary malignancies.
Cyclin-cyclin-dependent kinase complexes function by activating the machinery that allows the cell to replicate its DNA.
Cyclin-dependent kinase inhibitors such as CDKN2A and CDKN2B stop the cell from replicating its DNA response to a variety of signals, including DNA damage, cell-cell contact, cytokine release, and hypoxia.
Mutations in RB are common in urologic malignancies.
ATM plays a central role in sensing DNA damage, inducing S phase and G2M phase arrest, and DNA repair.

Apoptosis

Apoptosis is defined as programmed cell death. Apoptosis is a heavily dependent process
where mitochondria play a central role. An increase in mitochondrial membrane permeability
is a general observation. It is not known if mitochondria are absolutely necessary for
apoptosis, although they certainly participate in apoptosis, and may be necessary for
apoptosis in response to certain apoptotic stimuli. P53 and p21 are pro-apoptotic whereas
the bcl-2 family can be both pro- and anti- apoptotic.

The Bcl-2 family is a large family of proteins, some of which are anti-apoptotic, and some of
which are pro-apoptotic. Their main mechanism of action is thought to be the regulation of
mitochondrial membrane permeability. Pro-apoptotic members of the Bcl-2 superfamily
increase mitochondrial membrane permeability, whereas anti-apoptotic members of the
family act to oppose this increase. Increased mitochondrial membrane permeability allows
pro-apoptotic proteins into the cytoplasm e.g. caspases

Apoptosis may be stimulated by extracellular (death receptors e.g. FAS) or
intracellular (p53, p21, survivin). Results in mitochondrial permeability,
activation of caspses. Caspase 3 and 7 executioner caspases.
Principles of radiotherapy

Definition
Therapeutic use of ionising radiation for the Rx of malignancy

Radioisotopes
Beta emission (electrons) and gamma rays.
Examples iodine-125, palladium- 103, caesium-137

External Beam RT
Initially cobalt machines in 1950s
Later linear accelerators – stream of electrons accelerated with microwaves. Collision with tungsten generates X-rays. X-rays stream of high energy photons; identical to gamma rays, although term gamma ray reserved for photons from radioisotopes
Cyclotrons produce beams of protons and neutrons but expensive X-rays liberate electrons from tissue molecules – lead to secondary oxygen dependent damage to DNA. Leads to;
(i) DNA repair – most common outcome
(ii) Immediate cell death via apoptosis in a small number of normal cells (myeloid, lymphoid, germ cells)
(iii) **Death during next cell division.** Response therefore may be delayed in slow growing tumours.

Fractionation allows efficacious tumour kill without exceeding tolerance of surrounding structures. Advantages (4Rs)
(i) Recovery – allows normal cells time to recover from sublethal damage. Usually more efficient in normal cells compared with cancer cells
(ii) Reoxygenation – tumours cells often have hypoxic central cores. Reducing total number allows more oxygen dependent killing
(iii) Reassortment – Kill most effective in cells just about to divide (in G2 or S-phase). Re-application of RT to same tumour targets new population at sensitive stage
(iv) Repopulation – Allows repopulation of normal rapidly dividing cells such as bowel. Evidence to suggest that some tumours experience ‘accelerated repopulation’ limiting effect of RT*
(v) Intrinsic radiosensitivity ‘5th R’
SCC and adenocarcinoma similar radiosensitivity
Seminoma/lymphoma exquisitely radiosensitive
Melanoma, glioma and sarcoma radioresistant

Ability to deliver maximum dose related to tolerance of normal surrounding tissue. Explains development of conformal RT (multileaf collimators) to ‘shape’ shape the RT to the target tumour. Further advance IMRT (intensity modulated) uses complex software to dose according to location (ie. Rectal and urethral sparing in CaP)

* Development of accelerated hyperfractionation designed to combat accelerated repopulation phenomenon. Acceleration reduces time between Rx, but recovery reduced and toxicity increased.
Hyperfractionation designed to combat increased toxicity by reducing
dose. [CHART = continuous hyperfractionated - 12 days vs. 6 weeks proven efficacy in lung cancer]

NB. 1 gray is the absorption of one joule of energy

Complications of radiotherapy
Desquamation
Temporary cessation in production of epithelial cells
Skin thinning/ulceration 2 weeks after RT
Diarrhoea/bleeding 5 days after RT
Recovery depends on concentration of surviving stem cells
Infertility
3-6 Gy a/w development of infertility
Obliterative endarteritis
Lymphoedema
Late malignancy
Haematological malignancy > solid tumours
Increased risk a/w co-administration with alkylating agents