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

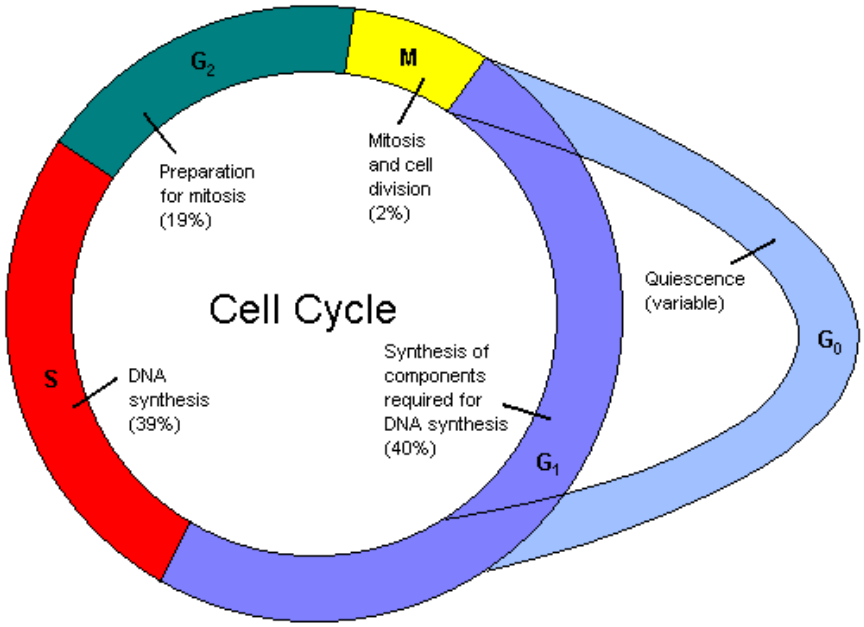
Types of cytotoxic drugs (6)

- Alkylating agents
  - *Cyclophosphamide*
  - *Cisplatin*
- Antitumour metabolites
  - *Gemcitabine*
  - *Methotrexate*
  - *5 FU*
  - *Mercaptopurine*
  - *Thiouracil*
- Antitumour antibiotics
  - *Doxorubicin/epirubicin*
  - *Mitomicin C*
  - *Bleomycin*
- Plant derived agents
  - *Vincristine & vinblastine*
  - *Docetaxel& Paclitaxel*
  - *Etoposide*
- Biological agents
  - *BCG*
  - *Interferon*
  - *Tyrosine kinase inhibitors*
  - *Bevacizumab*
- Hormonal agents
  - *Tamoxifen*
  - *Oestrogens*

CHEMOTHERAPEUTIC AGENTS AND THEIR MODES OF ACTION

Class	Example	Mode of action
Antimetabolites	Antifolates: MTX, 5FU	Inhibit steps in one carbon metabolism for purine synthesis – MTX inhibits dihydrofolate reductase, 5FU inhibits thymidylate synthetase
	Purine analogs: 6-mercaptopurine	Inhibit de-novo purine synthesis
Antibiotics	Bleomycin	Causes breaks in DNA
	Doxorubicin	Interferes with topoisomerase II and causes DNA breaks
	Mitomycin C	Crosslinks DNA
Platinum analogs	Cisplatin	Binds to DNA and forms DNA adducts
Alkylating agents	Melphalan, chorambucil, cyclophosphamide	Binds to DNA and forms DNA adducts
Vinca alkaloids	Vincristine, vinorelbine	Binds to tubulin causing mitotic arrest
	Paclitaxel	Binds to microtubules
	Etoposide	Interferes with topoisomerase II and inhibits nucleoside transport
Topoisomerase inhibitors	Camptothecin	Inhibits topoisomerase I and unraveling of DNA before replication fork
Acridine dyes	Amsacrine	Intercalates DNA causing DNA breaks
Retinoids	Retinol	? Causes differentiation of malignant cell

The 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*

<u>Pharmacotherapy</u>

Dosed vs. g/mg per square metre surface area

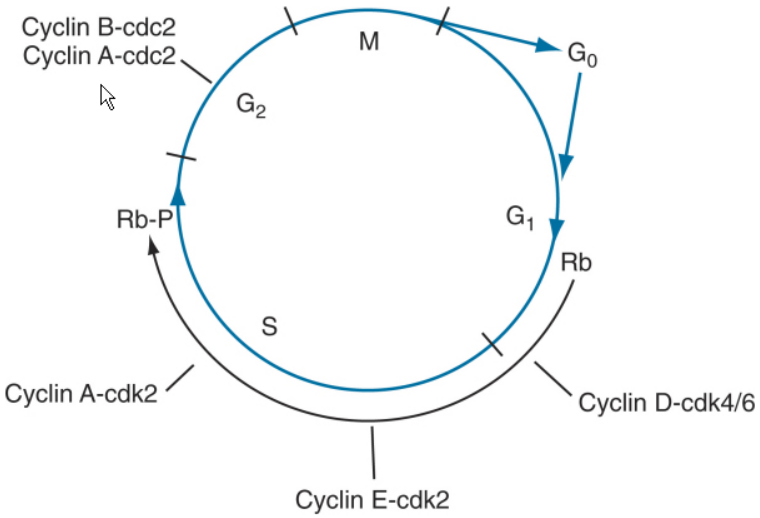
Maximum dose limited by :

- Toxic effects on rapidly dividing normal cells (bone marrow/intestine)
- Renal and liver function

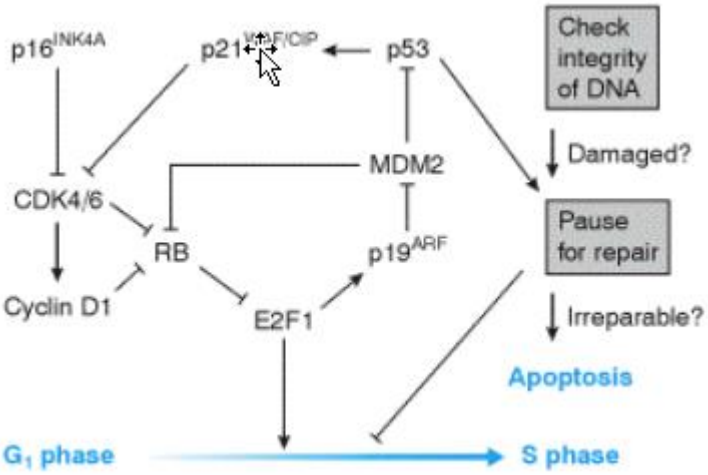
Hepatic function important for epirubicin, mitoxantrone, methotrexate, vinca alkaloids. Renal function important for cisplatin, methotrexate etc.

Selected complications	
Tissue destruction	Vinca alkaloids, doxaorubicin
Bone marrow toxicity	All agents
N & V (CTZ)	Cisplatin, cyclophosphamide, doxorubicin
Mucositis	Methotrexate
Diarrhoea	5 FU and cyclophosphamide
Hair loss	Doxorubicin, cyclophosphamide, etoposide, vincristine and paclitaxel
Leukaemia	All alkylating agents. Usually leukaemia – new solid tumours very rare
Infertility	Usually alkylating agents

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 (phopsphorylation) - 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

	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 G_1S and G_2M.

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.

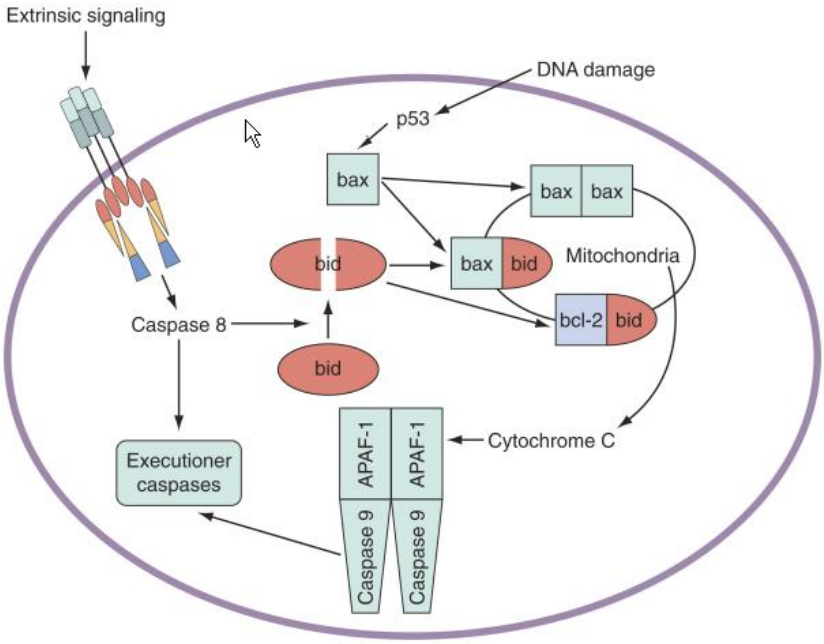
ATM plays a central role in sensing DNA damage, inducing S phase and G2M phase arrest, and DNA repair.

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 caspases. Caspase 3 and 7 executioner caspases.


Extrinsic signaling
DNA damage
p53
bax
bax bax
bid
bax bid
Mitochondria
bcl-2 bid
Caspase 8
bid
Executioner caspases
APAF-1
APAF-1
Cytochrome C
Caspase 9
Caspase 9

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