



Cancer chemotherapy

Definitions

Cancer:

A disease in which there is uncontrolled multiplication and spread within the body of abnormal forms of the body's own cells

Cancer = malignant neoplasm = malignant tumour

Neoplasm means “new growth”

Distinguishing characteristics from normal cells

- Uncontrolled proliferation
- Lack of differentiation and loss of function
- Invasiveness
- metastasis

Benign tumours



- Exhibit uncontrolled proliferation but lack the other 3 properties

Is it generally true that malignant cells proliferate faster than normal cells?



Let us examine some typical examples

Normal cells

Nerve cells: Have little or no ability to divide and proliferate

Bone marrow and GIT epithelium: have rapid and continuous division

Malignant cells



Some malignant cells multiply slowly:
Plasma cell tumours

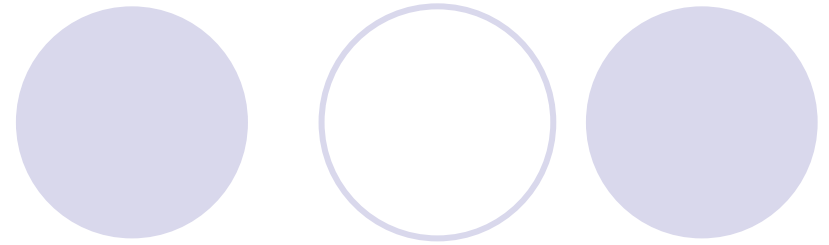
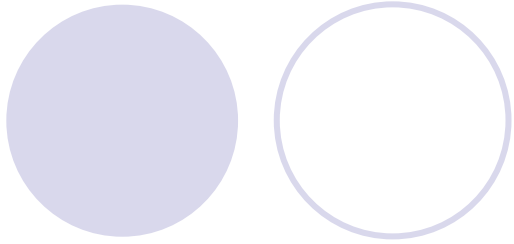
- Some malignant cells multiply fast: e.g. cells of the Burkitt's lymphoma

What is the difference?

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Consider the liver

- normally only a very small proportion of the cells are undergoing division at any time.
- If a portion of the liver is removed the remaining part will divide fast and continuously until the original size is regained
- In the rat if $2/3$ of the liver is excised the original size is regained in 2 weeks.



- Growth then stops
- Growth is regulated by processes not well understood
- Malignant cells are not subject to this regulation



The cell cycle

Positive regulatory factors

Growth factors

- Stimulate the cell to start on the cell cycle

Cyclins and cyclin-dependent kinases (cdks)

- Cyclins bind to and regulate the cdks which in turn control the enzymes of the cell cycle

Negative regulatory factors



- they are proteins which bind to the cdks and inhibit their action
- they are products of different genes
- e.g p53 gene, retinoblastoma (Rb) gene
- they act as super brakes of the cell cycle
- If DNA is damaged the inhibitors halt the cell cycle
- Repair takes place
- If repair fails, apoptosis is initiated

The genesis of tumours



DNA mutations (acquired or inherited)

2 types genetic changes can lead to cancer:

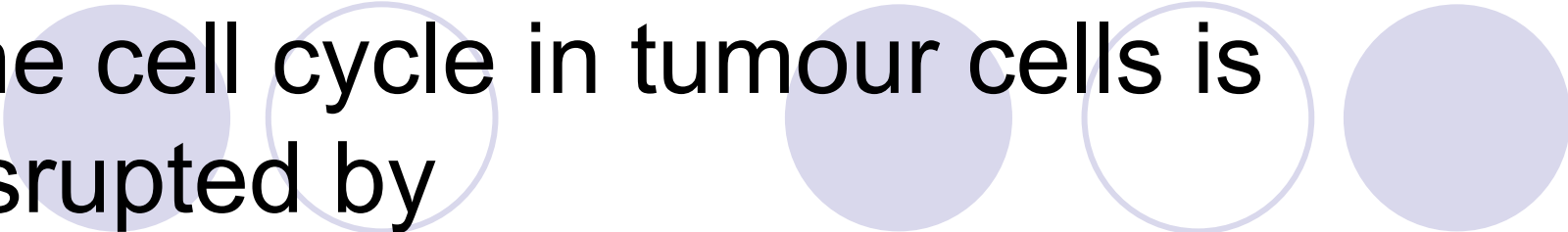
(1) inactivation of tumour suppressor genes

(anti-oncogenes) e.g p53 gene

- many human cancers are associated with mutations of the p53 gene

(2) Activation of proto-oncogenes to oncogenes

The cell cycle in tumour cells is disrupted by



- Abnormal growth factor function or
- Abnormal cyclin/cdk function or
- Abnormal DNA synthesis as a result of oncogene activity or
- Abnormal decrease of –ve regulatory factors due to mutation of tumour suppressor genes



Anticancer Chemotherapy

Problems of chemotherapy

- Lack of highly selective toxic agents
- Unlike viral, bacterial and fungal infections there are no obvious selective drug targets
- Many anticancer agents affect rapidly dividing normal cells (Bone marrow, gut epithelium, spermatogenic cells, lymphoid tissue, hair follicles, foetus).

Adverse effects of anticancer drugs

- Usually severe
- Need supportive drug therapy
- Need intensive nursing care
- Two types (immediate and delayed)



Immediate reactions

Nausea and vomiting (cisplatin)

Use anti-emetic drugs

- 5-HT₃ receptor antagonists (ondansetron, granisetron)
- High doses of metoclopramide (i.v) + dexamethasone or lorazepam
- Metoclopramide causes extrapyramidal side effects in children and young adults
- Substitute with diphenhydramine



- Local irritation (pain & inflammation)
Due to extravasation at injection site
(doxorubicin)

Delayed effects



Bone marrow depression (most anticancer drugs)

- Occur 7-14 days after a single dose
- Indicated by decrease in platelet and leukocyte counts
- Neutrophils are most susceptible
- May predispose to septicaemia
- May be used as an indicator of the efficacy of treatment

Management of severe myelosuppression

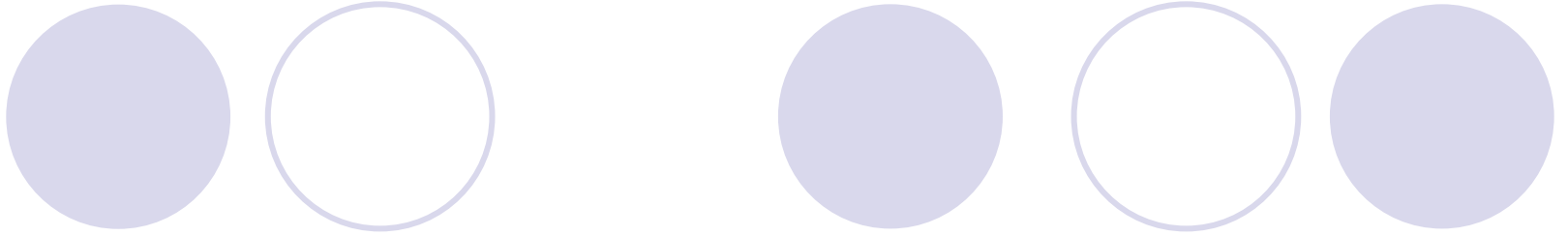


- Concurrent administration of granulocyte colony stimulating factor (GCSF)
- Or remove some of the patient's bone marrow and replace it afterwards
- Or administer molgramostim, then harvest stem cells from the blood and multiply them *in vitro* with haemopoietic growth factors
- Introduce a mutated multi-drug resistance gene into the extracted bone marrow (marrow cells and not cancer



Immunosuppression

- due to marrow depression
- direct effect on lymphocytes
- low resistance to infection
- reduced immunological response to the neoplasia itself



GIT disturbances (methotrexate)

- Mucosal ulceration
- Bleeding
- Diarrhoea

Allopecia or epilation (doxorubicin)

- hair loss
- reversible

Neurotoxicity (vinca alkaloids)

- manifests as peripheral neuropathy
- constipation and ileus
- loss of sensation in the fingers and toes

Hepatic damage

- due to toxic metabolites

Teratogenicity (avoid in pregnancy)

Impaired growth in children



Infertility

- premature menopause (women)
- azoospermia in men (irreversible)
- Mutagenesis(alkylating agents)
- Cause secondary malignancies
- Acute myeloid leukaemia
- bladder cancer after treatment with cyclophosphamide

Anticancer drugs



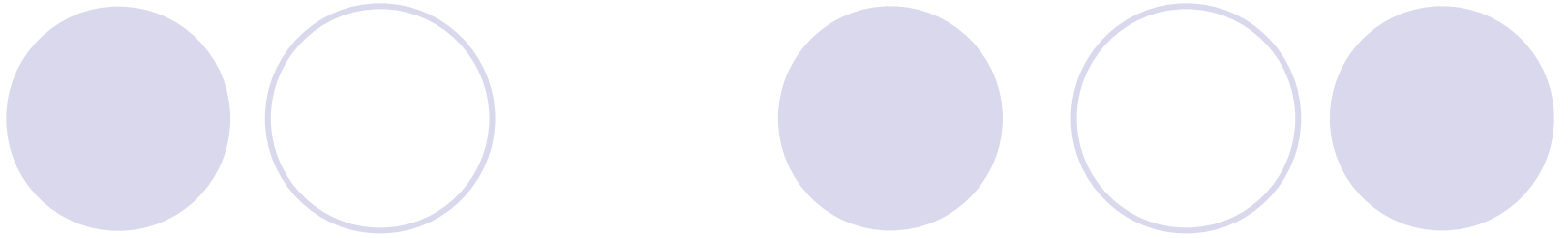
Can be divided into 2 groups:

- Cell-cycle phase dependent
- cell-cycle phase independent



Cell-cycle phase dependent

- Act mainly on cells in certain phases of the cell cycle
- do not act on the G_0 phase
- the cell kill is greater if the drug is given in repeated fractions rather than a summated single dose
- most effective in tumours with a large proportion of cells that are actively dividing



- Most are anti-metabolites:
- mercaptopurine, methotrexate, fluorouracil (S phase)
- Vinca alkaloids and Taxanes (M phase)

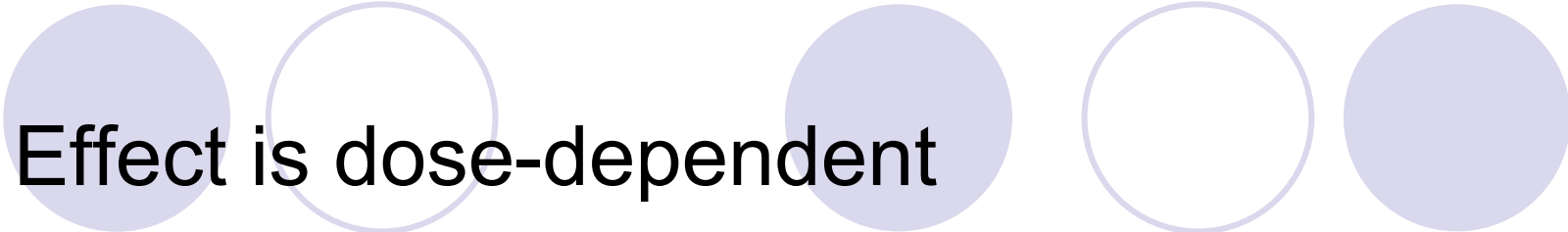


Application to cell culture

- The percentage of surviving cells declines steeply at first with increasing dose
- increasing the dose further reaches a plateau where further increase in dose produces no further increase in cell death

Cell-cycle phase-independent drugs

- eg cyclophosphamide, doxorubicin, cisplatin
- Act on cells in any phase of the cycle
- have a slight effect on the G_0 phase
- equally effective in tumours where the growth fraction and mitotic index are low

- 
- Effect is dose-dependent
 - degree of kill is proportional to the dose given
 - a bolus dose is as effective as a fractionated dose of the same amount
 - survival of cells in culture declines progressively with increasing dose

Treatment of large solid tumours

- They are less responsive to drugs because of poor vascularization
- many cells are in the G_0 phase
- Use cell-cycle phase independent drugs first:
 - -to reduce cell numbers
 - -to promote recruitment of cells into the growth phase of the cell cycle
 - -will create susceptibility to cell-cycle



antimetabolites


- Block or subvert one or more of the metabolic pathways involved in DNA synthesis
- Folate antagonists
- purine analogues
- pyrimidine analogues

Folate antagonists



Methotrexate

- inhibits dihydrofolate reductase
- used to treat a wide variety of solid and blood tumours
- used to treat choriocarcinoma

- 
- Causes bone marrow depression
 - may cause pneumonitis
 - Damages epithelium of the GIT
 - High doses may be nephrotoxic due to:
 - precipitation of the drug or metabolite
 - Normal cells affected by high doses can be “rescued” by folinic acid (leucovorin or N5-methyl THFA)

Purine analogues



Mercaptopurine

- Used in combination with other drugs in the maintenance treatment of acute leukaemias
- Metabolized in the liver by xanthine oxidase
- Allopurinol is used to inhibit its metabolism and increase its cytotoxic action



Fudarabine

- Metabolized to triphosphate
- Triphosphate is incorporated into both RNA and DNA
- Inhibits DNA polymerase
- Inhibits both replication and repair of DNA

Causes myelosuppression



Pentostatin

- Inhibits adenosine deaminase
- Adenosine deaminase catalyses deamination of adenosine to inosine
- Interferes with critical pathways in purine metabolism
- Has a significant effect on cell proliferation

Others



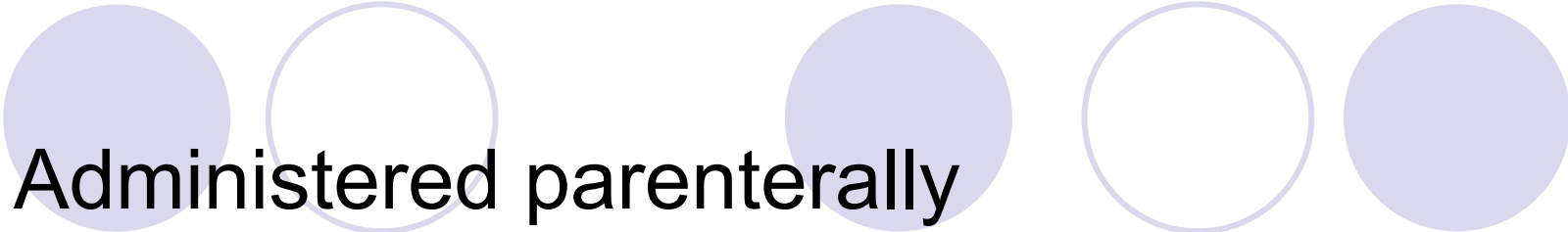
- Thioguanine – analogue of mercaptopurine
- Azathioprine (analogue of mercaptopurine) – used as an immunosuppressant
- Claribine



Pyrimidine analogues

Fluorouracil

- Converted to fluorodeoxyuridine monophosphate (FDUMP)
- Interferes with thymidylate synthesis
- Blocks DNA synthesis

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- Administered parenterally
 - Palliative treatment of different types of malignancies
 - Very good for colon cancer
 - Caused GIT epithelial damage, myelotoxicity and cerebellar disturbances

Tomudex – a newer thymidylate synthesis inhibitor

Cytarabine (cytosine arabinoside)


- Nucleoside analogue of 2'-deoxy-cytidine
- Phosphorylated to triphosphate
- Inhibits DNA polymerase
- Good for inducing remission in acute leukaemias
- Causes myelosuppression




Alkylating and related agents

- Contain chemical groups which have the property of forming covalent bonds with suitable nucleophilic substances in the cell
- Form ions which react with electron donors eg amines, -OH, -SH groups

- N7 of guanine is strongly nucleophilic
- Probably the main target for alkylation in DNA
- N1 and N3 of adenine and N3 of cytosine may also be affected

- 
- Most of the anticancer alkylating agents have 2 alkylating groups
 - Can react with 2 gps to cause intra- and inter-chain cross-linking
 - Interferes with both replication and transcription

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- main action occurs during replication when some parts of DNA are unpaired and more susceptible to alkylation
 - Effects manifest during S phase, resulting in a block at G₂
 - Result in apoptotic cell death

Adverse reactions

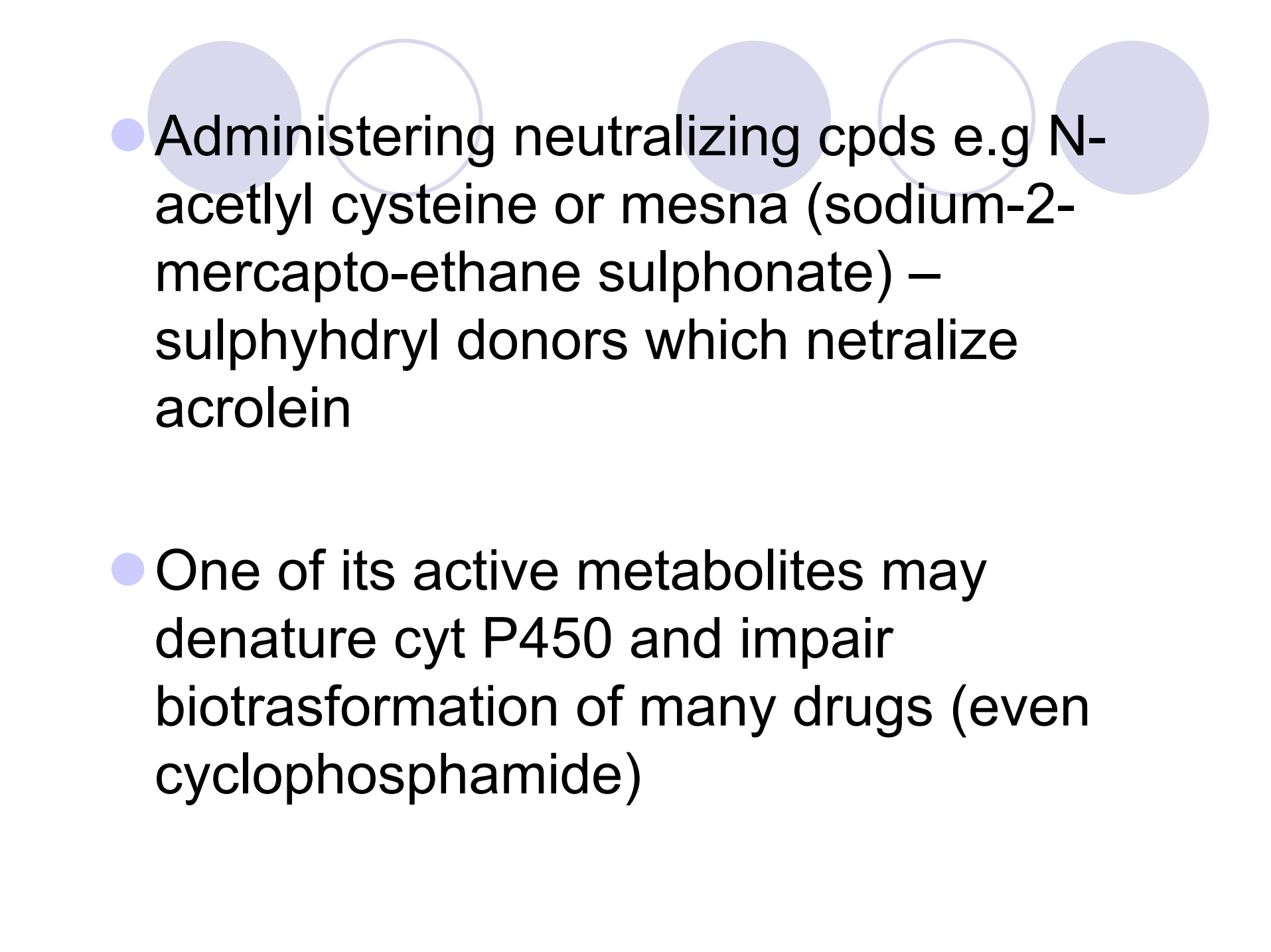


- Bone marrow depression
- GIT disturbances
- Depression of gametogenesis
- Increased risk of acute non-lymphocytic leukaemia and other malignancies

Cylophosphamide



- Wide spectrum antitumour drug
 - Given by injection (i.m, i.v) or orally.
- Its metabolite (acrolein) is irritant to the bladder.**
- Causes haemorrhagic cystitis
 - Can be avoided by administration of a lot of fluids

- 
- Administering neutralizing cpds e.g N-acetyl cysteine or mesna (sodium-2-mercapto-ethane sulphonate) – sulphhydryl donors which neutralize acrolein
 - One of its active metabolites may denature cyt P450 and impair biotransformation of many drugs (even cyclophosphamide)



Ifosphamide

- Structurally similar to cyclophosphamide
- Activated in liver
- causes haemorrhagic cystitis, leukopenia, nephrotoxicity, CNS disturbances



- Different pharmacological & toxicological properties

Used to treat:

- Germ cell testicular cancer
- Carcinoma of cervix, lung
- Hodgkin's and non-Hodgkins lymphomas
- sarcomas

Chlorambucil



- Slowest acting nitrogen mustard
- Treatment of choice for chronic lymphatic leukaemias
- Others are mustine, melphalan, mechlorethamine

Estramustine

- Mustine + oestrogen
- Has both cytotoxic and hormonal action

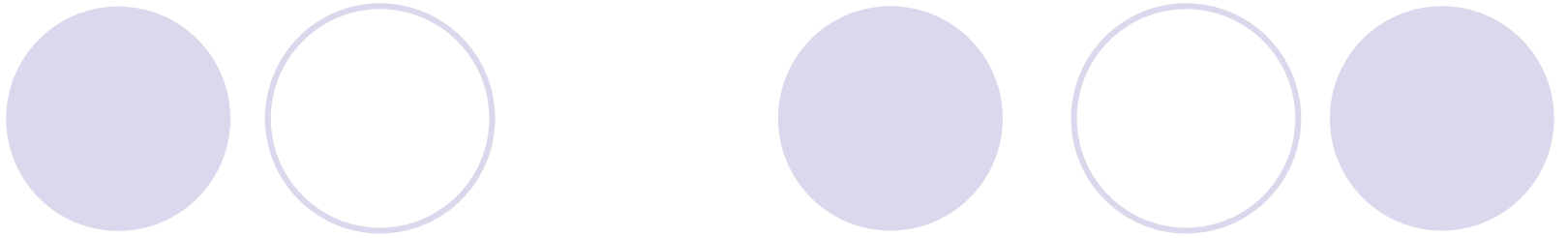
Nitrosoureas



2 types:

(a) 2-chloroethylnitrosoureas (CNU)

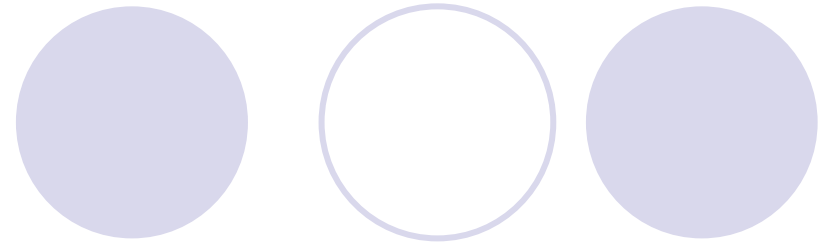
- Carmustine, lomustine, semustine
- Lipid soluble and can cross BBB
- Used against tumours of the brain and meninges
- Act on non-dividing cells (G_0)
- Cause delayed bone marrow depression (cumulative myelotoxicity)



(b) methylnitrosourea (MNU)

- Streptozotocin (naturally occurring nitrosourea)
- Toxic to pancreatic beta cells
- Used for treatment of pancreatic cell carcinoma

Busulphan (Alkyl sulfonate)



- Has selective effect on bone marrow
- In low doses it depresses formation of granulocytes and platelets
- In high doses it depresses formation of red cells
- Has little or no effect on lymphoid tissue or the GIT
- Used to treat chronic granulocytic leukaemia



Procarbazine

- Hydrazine derivative
- Binds covalently to DNA and promote single strand breaks
- Combined with other drugs for the treatment of the Hodgkin's lymphoma
- Causes a disulfirum-like effect if taken with alcohol



Cisplatin

- Used for treatment of tumours of testis and ovary
- Given by slow iv injection or infusion
- Seriously nephrotoxic (administer a lot of fluids and diuretics)
- Causes very severe nausea and vomiting



- Tinnitus & hearing loss in high frequency range
- Peripheral neuropathies
- Hypeuricaemia
- Anaphylactic reactions

Carboplatin



- Derivative of cisplatin
- Has less severe nephrotoxicity, neurotoxicity and ototoxicity
- Less severe nausea and vomiting
- More myelotoxic



Darcabazine

- Prodrug
- Activated in the liver to an alkylating agent
- Blocks DNA, RNA and protein synthesis
- Used to treat malignant melanoma

NATURAL PRODUCTS




Inhibitors of mitosis

Vinca alkaloids:

Vincristine, vinblastine, vindesine,
vinorelbine


- Prevent formation of microtubules
- Arrest mitosis in metaphase
- Inhibit other cellular activities that involve the microtubules eg leukocyte phagocytosis, chemotaxis and axonal

- 
- Used in combination with prednisolone to treat childhood leukaemias
 - Combined with mechlorethamine, prednisolone and procarbazine (MOPP) for the treatment of advanced Hodgkin's disease
 - Non-Hodgkin's lymphomas (in combination with cyclophosphamide, bleomycin, doxorubicin and prednisolone)

TAXANES



- Pacletaxel and docetaxel
- Derived from taxol (cpd obtained from the Pacific yew tree, *Taxus brevifolia*)
- Bind to microtubules and stabilize (freeze) them in the polymerized state
- Arrest mitosis in metaphase

- 
- Effective in malignancies resistant to vinca alkaloids
 - Useful for treatment of melanoma and cancers of the breast and ovary
 - Suppresses bone marrow
 - Causes cumulative neurotoxicity
 - Hypersensitivity reactions (require pre-treatment with corticosteroids & antihistamines)

Epipodophyllotoxins



Etoposide & teniposide

- Inhibit topoisomerase II
- Cause DNA double strand breaks
- Given iv

Etoposide:

- Wide spectrum anticancer activity
(Lung, testes, Hodgkin's disease etc)
- Testicular tumours (etoposide + bleomycin + cisplatin)
- Small-cell carcinoma of the lung (etoposide + cisplatin)



Adverse effects

- myelosuppression
- Repeated administration may cause peripheral neuropathy

Camptothecins

- Irinotecan & topotecan
- inhibit topoisomerase I
- Have less unwanted effects than most other anticancer agents
- Cause diarrhoea & reversible bone marrow depression



anthracyclines

Doxorubicin, idarubicin, epirubicin,
aclarubicin, mitozanthrone

- Inhibit topoisomerase II
- Inhibit both DNA and RNA synthesis

Doxorubicin



- Used for treatment of acute leukaemia, hodgkin's disease, CA of breast, ovary and small cell CA of the lung
- Given iv
- Extravasation at site of injection causes local necrosis
- Cumulative, dose-related cardiac damage leading to arrhythmias & heart failure



Mitozanthrone:

- Structurally related to doxorubicin
- Causes a dose-dependent cardiotoxicity
- Depresses bone marrow

Epirubicin is less cardiotoxic than doxorubicin

Dactinomycin (Actinomycin D)

- Intercalates DNA between adjacent guanosine-cytosine pairs
- Interferes with the movement of RNA polymerase along the gene
- Prevents transcription
- Inhibit RNA synthesis
- Also inhibits topoisomerase II
- Dactinomycin + methotrexate – (choriocarcinoma)

Bleomycins (bleomycin, plicamycin, mitomycin)

- Metal chelating glyco-peptide antibiotics
- Degrade preformed DNA
- Cause chain fragmentation and release free bases
- Inhibit repair of DNA



Bleomycin

- Given i.v or i.m
- Most effective in the G_2 phase and mitosis
- Also effective in the G_0 phase
- Used to treat testicular and ovarian cancers and squamous cell carcinoma

Testicular carcinoma

- Can be curative when used with vinblastine and cisplatin

Adverse reactions



- Little myelosuppression (less than other anticancer agents)
- Allergic reactions
- Mucocutaneous reactions
- Most serious side effect is pulmonary fibrosis (10 % of patients; fatal in 1%)

Mitomycin



- Activated by enzymes
- Generate a bifunctional alkylating agent
- Cross-links DNA
- Degrades DNA through formation of free radicals
- causes myelosuppression, kidney damage, lung fibrosis



Hormones

- Target tumours derived from hormone-sensitive tissues
- Some of these tumours are hormone dependent
- Their growth can be inhibited by:
 - hormones with opposing actions
 - hormone antagonists
 - inhibitors of hormone synthesis


Glucocorticoids (prednisolone)

- Inhibit lymphocyte proliferation
- Cause dissolution of lymphocytes
- Used in leukaemias and lymphomas
- Used with other anticancer agents as supportive agents to lower intracranial pressure
- Has antitumour activity against some solid tumours



Oestrogens

- Castration + oestrogen therapy is used for treatment of prostatic carcinoma
- Oestrogen antagonizes effects of androgens on the prostate
- Diethylstilboestrol (stilboestrol)
- Fosfesterol: metabolized by acid phosphatase to stilboestrol

- 
- Treatment of advanced breast cancer with wide spread metastases and not responding to tamoxifen
 - Oestrogens recruit resting mammary cancer cells into the proliferating pool of cells
 - Allow a greater killing efficacy of the cytotoxic drugs which are then given

Side effects: hypercalcaemia

Anti-oestrogens



Tamoxifen:

- 1st line hormonal treatment for hormone-dependent breast cancer
- Competitively blocks oestrogen receptors
- Inhibits transcription of oestrogen-responsive genes
- Retards oestrogen-dependent tumour growth



Progestogens (progestins)

- Management of endometrial neoplasms
- Suppresses production of oestrogen by endometrial cells
- 2nd line hormonal treatment for metastatic hormone-dependent breast cancer.
- Renal tumours

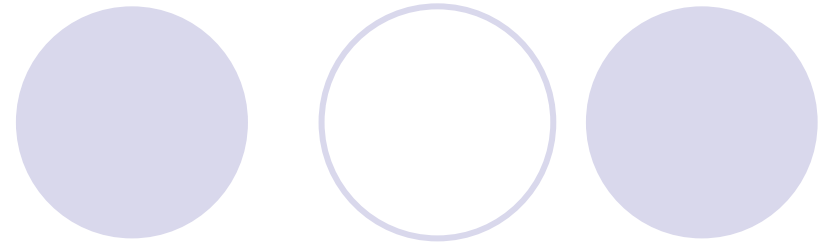
Drugs: megestrol, medroxyprogesterone

Gonadotrophin-releasing hormone analogues

Goserelin (GRH analogue)

- Used to inhibit gonadotrophin release
- Used to treat advanced breast cancer in premenopausal women
- Prostate cancer

Anti-androgens



- Flutamide, cyproterone (androgen antagonists)
- Prostate cancer



octreotide

- Analogue of somatostatin
- Used to treat various hormone-secreting tumours of the GIT eg VIPomas, glucagonomas, carcinoid syndrome, gastrinomas
- These tumours express somatostatin receptors
- Activation of the receptors decrease cell proliferation and hormone secretion

Adrenal hormone synthesis inhibitors



- Several agents which inhibit synthesis of adrenal hormones have effects in postmenopausal breast cancer

eg (1) formestane

- Inhibits the enzyme aromatase
- Interferes with the conversion of androgens to oestrogens

(2) Trilostane & aminoglutethimide

- Inhibit sex hormone synthesis at an early stage
- Replacement of corticosteroid is necessary



Radiotherapy & radioisotopes

Radiotherapy (X-rays, neutrons)

- Used for localized tumours
- Produce highly reactive free radicals that react with DNA
- Used in combination with cytotoxic drugs

Radioisotopes:

- Iodine (^{131}I) treatment of thyroid tumours
- ^{32}P for treatment of chronic myeloid leukaemia (as effective as busulphan)

Treatment schedules

- Determined from cell kinetic studies
- Use large intermittent doses (2-3 weeks in between) rather than small continuous doses
- Combination therapies increase cytotoxicity Vs cancer cells without necessarily increasing general toxicity
- Combination therapies decrease the possibility of the development of resistance to individual drugs