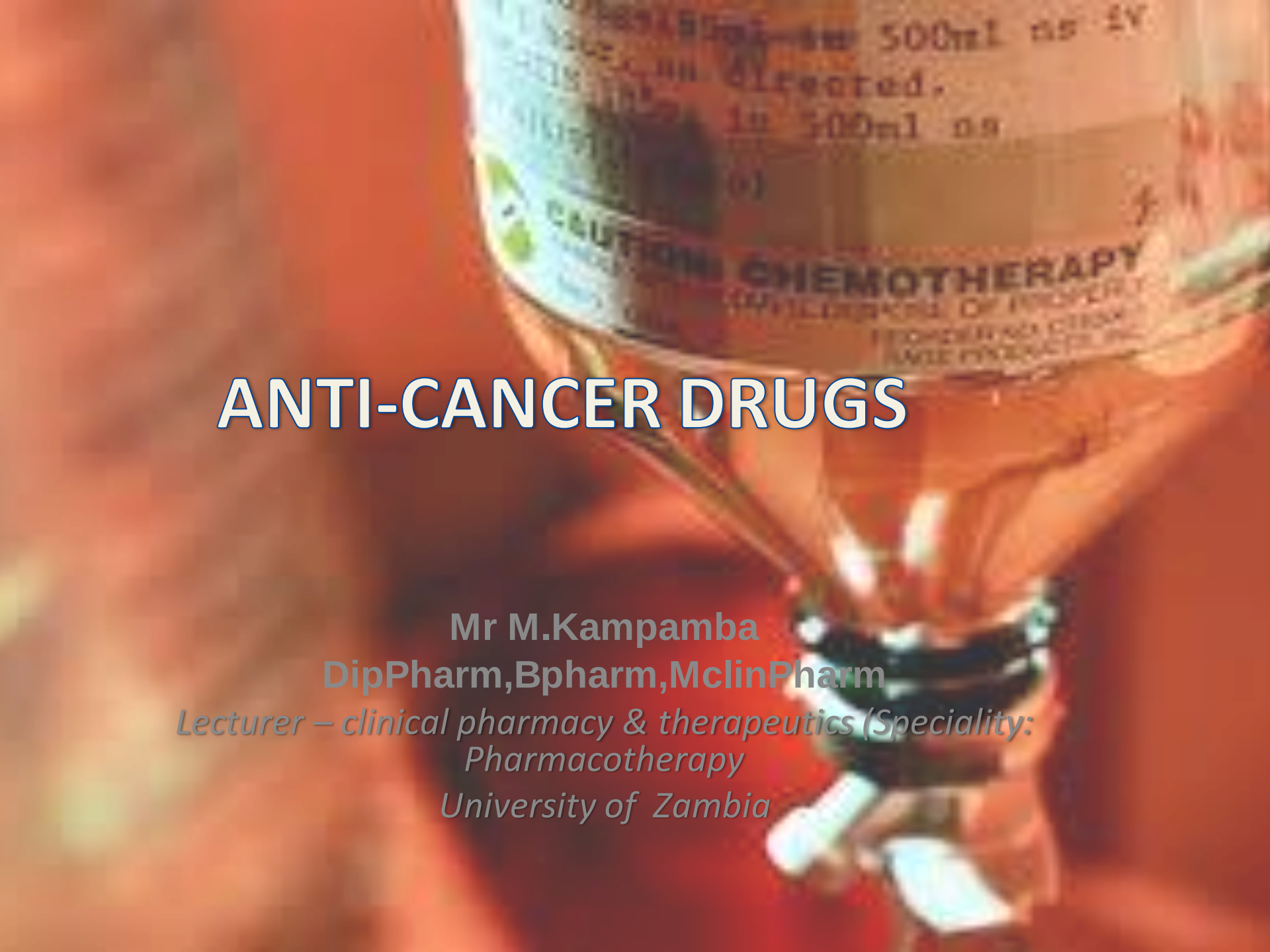

ANTI-CANCER DRUGS

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Objectives

By the end of this class, students should be able to:

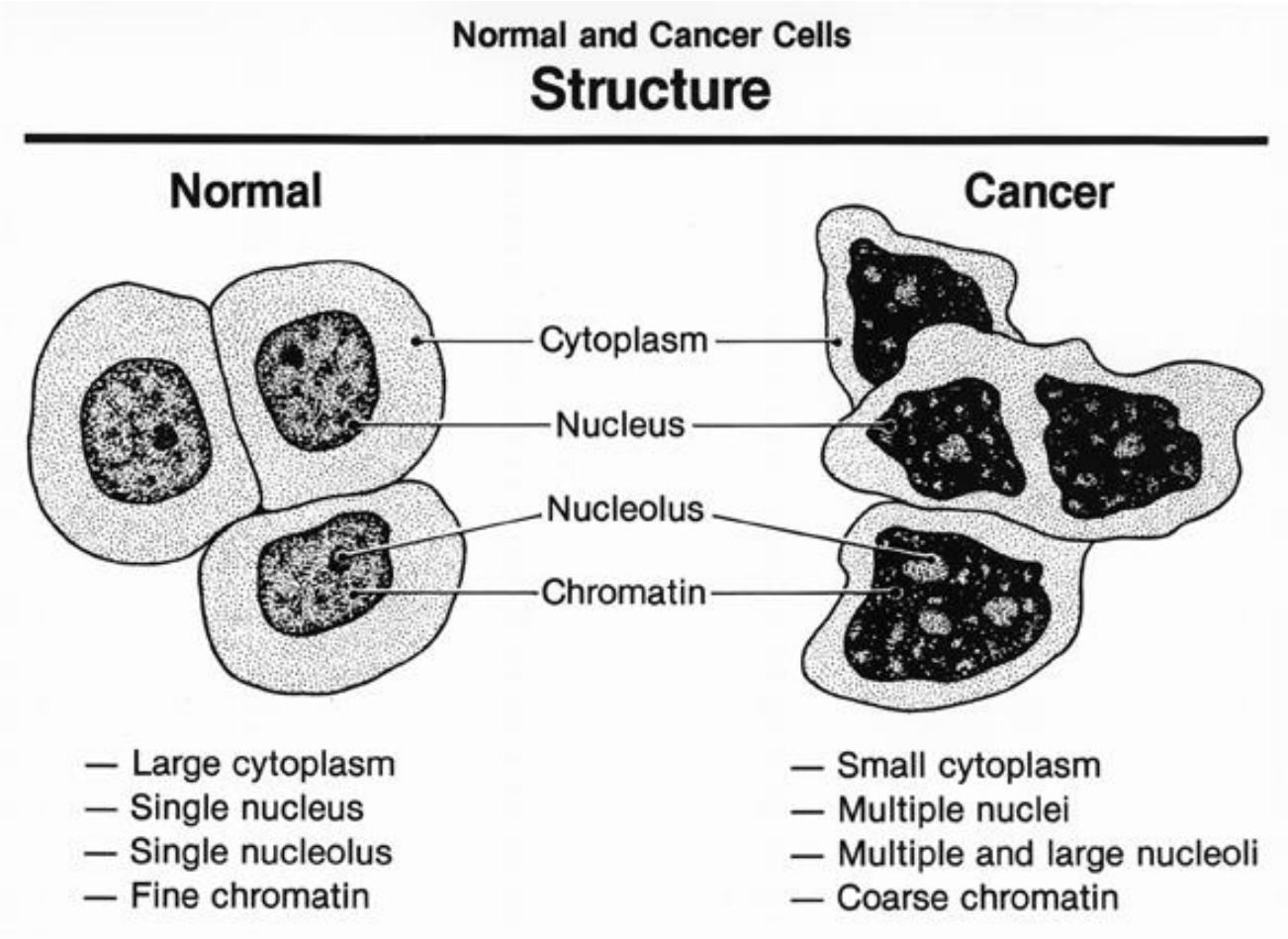
- Define cancer Chemotherapy
- State causes of cancer
- Classify anticancer drugs
- Discuss MoA for the different anti cancer drugs
- Discuss Common side effects and management/prevention for anticancer drugs.

Use of Chemotherapeutic agents in cancer disorders to kill, damage, or retard growth of cancer cells, (and those used to prevent or treat adverse drug effects)

- Definition: Cancer Chemotherapy is a medical treatment that uses drugs to target and destroy cancer cells in the body

- The primary goal of chemotherapy is to inhibit the growth, division, and spread of cancer cells, which are characterized by their uncontrolled and abnormal growth

Normal vs. Cancer Cells



Normal vs. Cancer Cells

- No Qualitative difference between malignant and normal cells
- However, Quantitative differences; cancer cells have:

  a) Rapid, uncontrolled rate of mitosis

  b) Rapid turnover of nucleoproteins

  c) High anabolic & low catabolic enzyme activity

  d) High dephosphorylating activity

  e) Undifferentiated structure & function

Important information

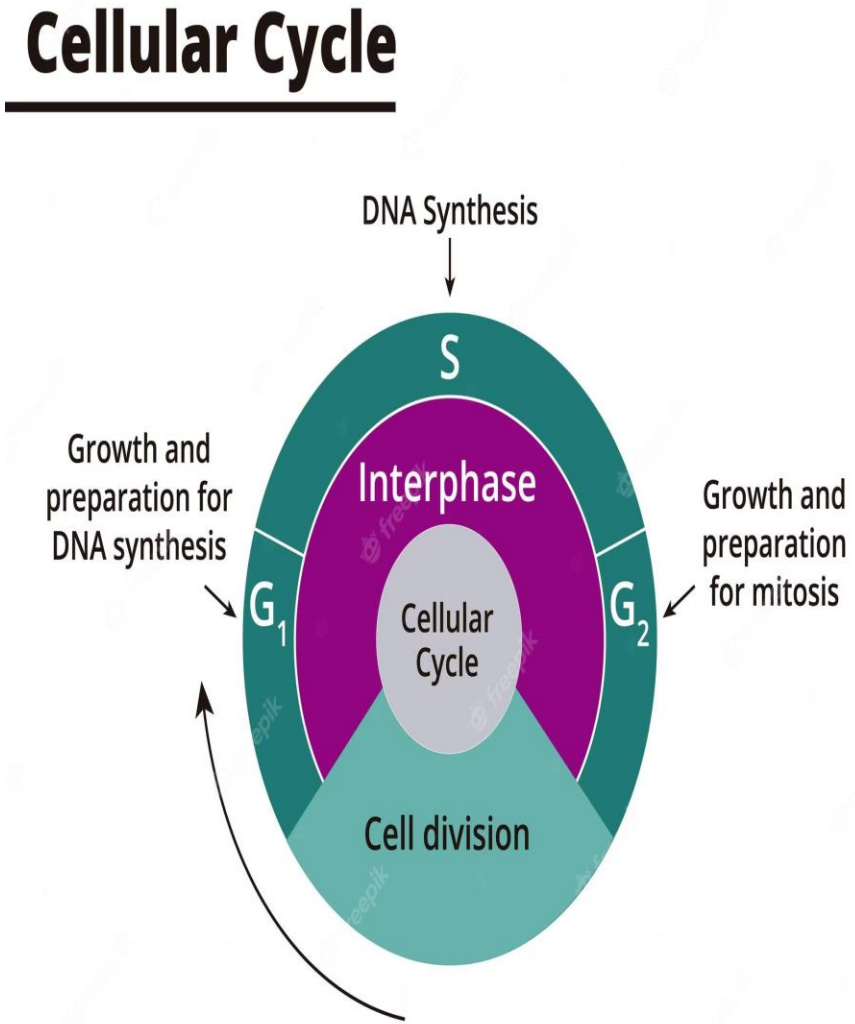
- Uncontrolled division of cells leading to a tumor formation
- Cancer cells have lost the normal regulatory mechanisms that control cell growth and multiplication
- **Benign** cancer cell stay at the same place
- **Malignant** cancer cells invade new tissues to set up secondary tumors, a process known as metastasis
- Chemicals causing cancer are called **mutagens**
- Cancer can be caused by chemicals, life style (smoking), and viruses
- Genes that are related to cause cancer are called **oncogenes**.
- Genes that become oncogenic upon mutation are called **proto-oncogenes**.

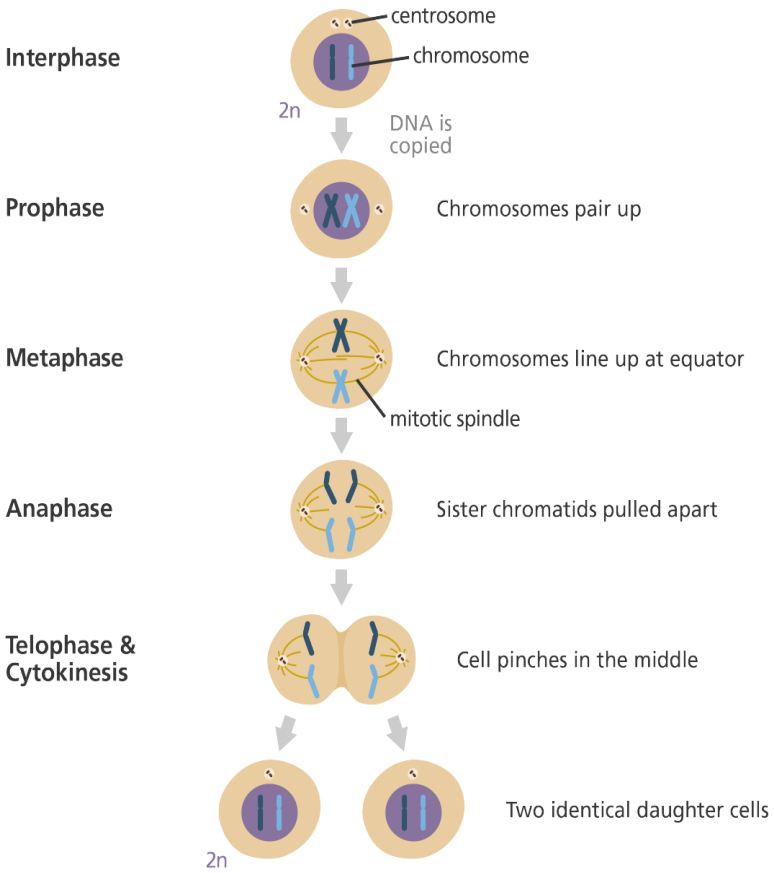
Classification of Cancers

1. **Hematologic malignancies:**
   - *involve bone marrow & lymphoid tissues;*
   - *include leukemias, lymphomas, and multiple myeloma*

2. **Solid neoplasms**
   - *Two major classifications: Carcinomas and Sarcomas.*
   - *Carcinomas derived from epithelial tissues (skin, mucous membrane, linings and coverings of viscera) - most common type of malignant tumors*
   - *Sarcomas derived from connective tissue (muscle, bone, cartilage, fibrous tissue, fat, blood vessels)*

Mitosis Revisited





2n = diploid

ANTICANCER AGENTS

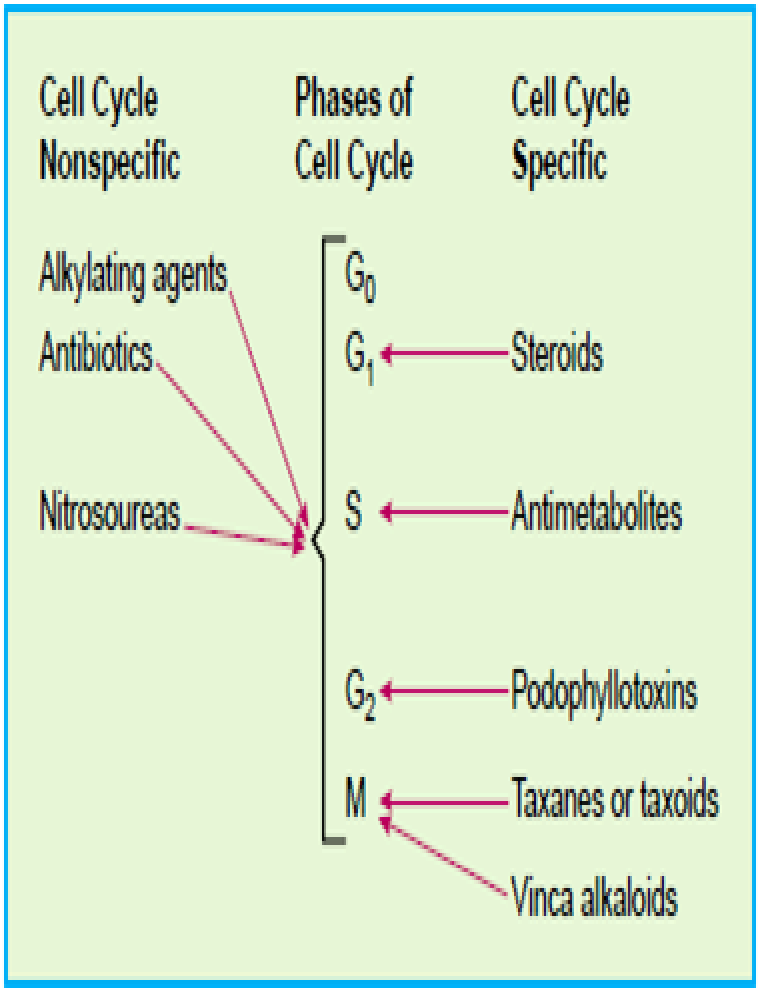
Classification of Anticancer Drugs

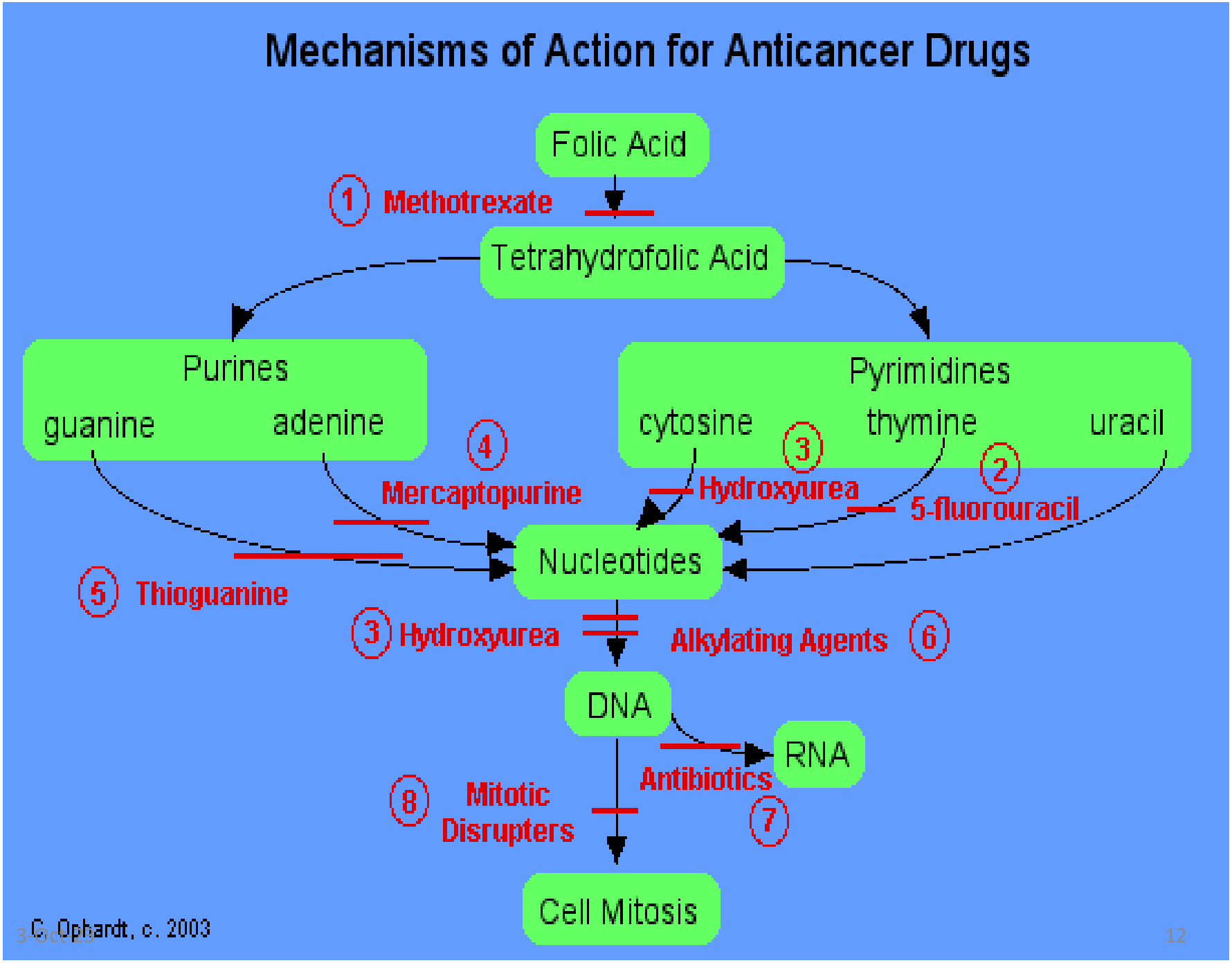
1. **Cell Cycle Specific agents (CCS)**: - are effective only against rapidly dividing (cycling) cells;

   e.g. Steroids, Anti-metabolites, Vinca-alkaloids, Taxanes, etc

2. **Cell Cycle Non-specific agents (CCNS)**: - kill whether resting or actively cycling cells;

   e.g. Alkylating agents, Antibiotics (e.g. Adriamycin, Dactinomycin), Nitrosoureas




Mechanisms of Action for Anticancer Drugs
Folic Acid
1 Methotrexate
Tetrahydrofolic Acid
Purines
guanine
adenine
Pyrimidines
cytosine
thymine
uracil
4 Mercaptopurine
3 Hydroxyurea
2 5-fluorouracil
Nucleotides
5 Thioguanine
3 Hydroxyurea
Alkylating Agents 6
DNA
RNA
Antibiotics 7
8 Mitotic Disrupters
Cell Mitosis
C. Ophardt, c. 2003

1. Alkylating Agents

- Chemical substances containing highly reactive Alkyl groups;

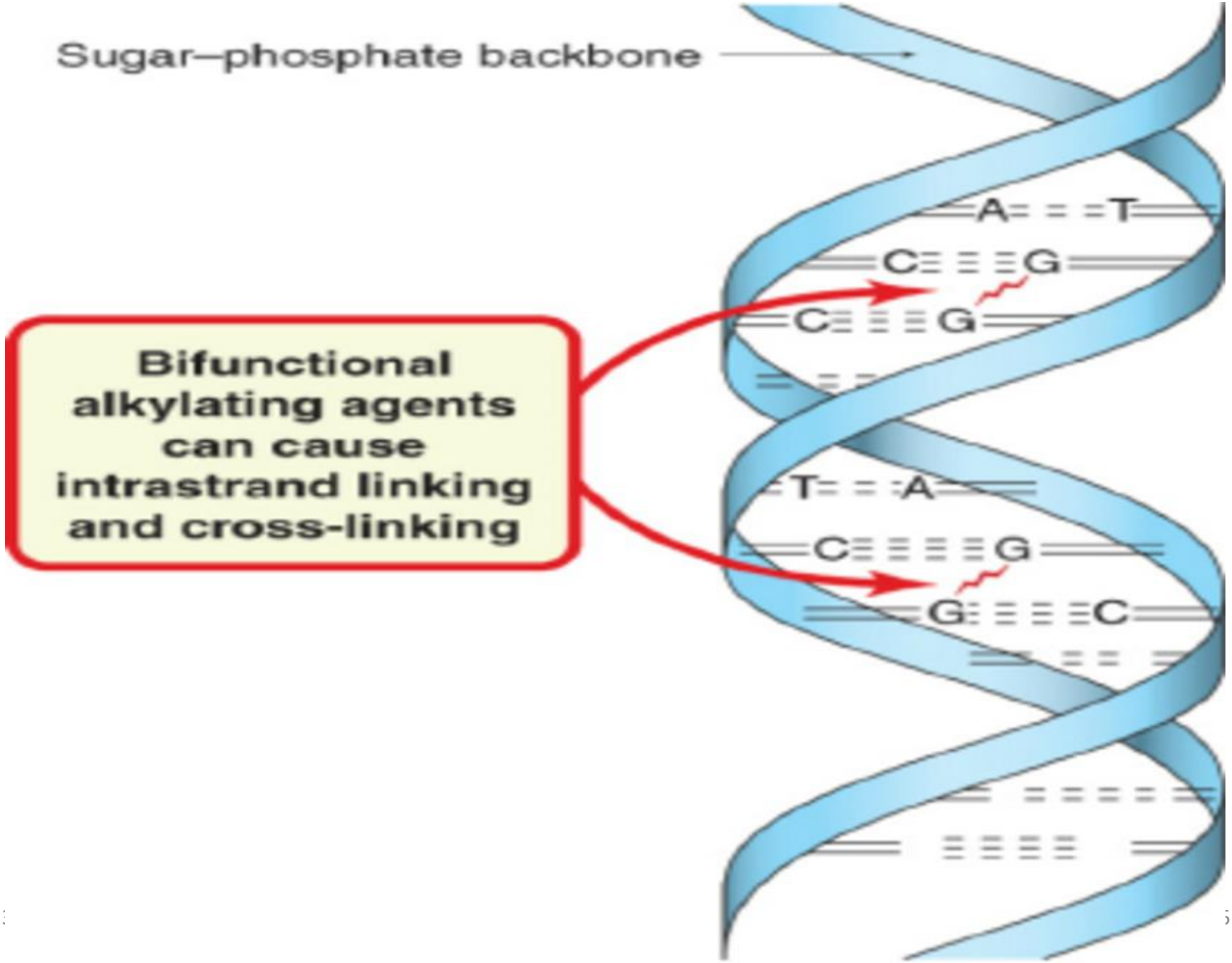
- **Mechanism of action:** Transfer active alkylating groups to cell constituents *(mainly DNA, proteins and enzymes)* inhibiting their function
- The N7 of guanine is main target for alkylation in DNA (alkylation of adenosine or cytosine also occurs to lesser degree)
- Bifunctional agent, i.e. react with two groups, causing intra- or inter chain cross linking.

CCNS; effective against slow growing neoplasms

- After alkylation, DNA is unable to replicate and therefore can no longer synthesize proteins and other essential cell metabolites.

Other Effects= Excision of guanine base or pairing of G with T instead of C occurs

- Consequently, cell reproduction is inhibited and the cell eventually dies
- Alkylating agents=not cell cycle specific but cells are most susceptible to alkylation in late G1 & S phases of cell cycle & express block in G2


Sugar–phosphate backbone
Bifunctional alkylating agents can cause intrastrand linking and cross-linking
A
T
C
G
C
G
T
A
C
G
G
C

Cont…

- Inhibit the division of rapidly dividing cells including ; cancerous cells , normal cells (bone marrow, lymphoid tissue, mucosal surface of GIT, hair follicle, gonads)
- Cause leukopenia, thrombocytopenia, alopecia, sterility sterility, development development of vesicles vesicles on skin, mucosa & eyes
- Nausea & vomiting

Examples of Alkylating agents

Nitrogen mustards:

- *Mechlorethamine*
- *Cyclophosphamide*
- *Chlorambucil*
- *Melphalan*
- *Ifosfamide*

Alkyl sulphonates:

- *Busulphan*
  (used in bone marrow tumors)

Nitrosureas:

- *Carmustin*
- *Lomustin*
- *Semustin*

Platinum compounds

- *Cisplatin*
- *Carboplatin*
- *Oxaliplatin*

Tetrazines

- *Dacarbazine,*
- *Mitozolomide*
- *Temozolomide*

Aziridines:

- *Thiotepa,*
- *Mitomycin*
- *Diaziquone*

A- Nitrogen Mustards

Cyclophosphamide

- The most commonly used alkylating agent is inactive until metabolized in the liver by the P450 mixed-function oxidases.
- It has a pronounced effect on lymphocytes and can be used as an immunosuppressant.

Given orally, i.v, im

Uses:

- Lymphomas
- Breast cancer,
- In Burkitt's lymphoma,
- Myeloma
- chronic leukemias
- Certain autoimmune disease

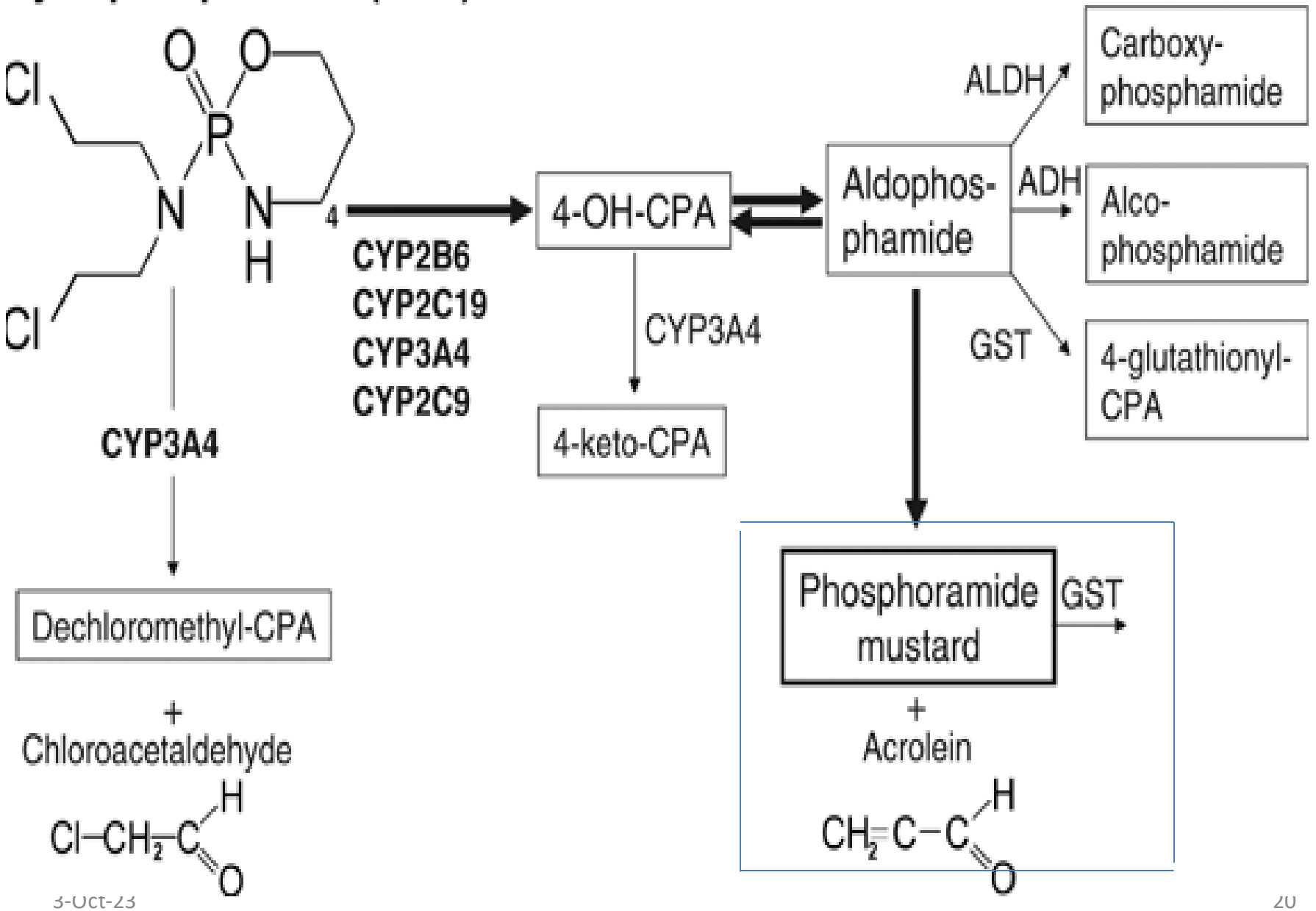
ADR:- Nausea , vomiting, bone marrow depression and

haemorrhagic cystitis

Haemorrhagic cystitis

- due to ***acrolein*** (metabolite)
- ameliorated by ↑fluid intake and by taking sulfhydryl donors such as ***sodium-2-mercaptoethane sulfonate***, or ***mesna***
- Mesna + acrolein = non toxic compound
- Mesna = used during treatment with cyclophosphamide to ↓ its toxicity

Cyclophosphamide (CPA)



B- Nitrosoureas

Lomustine(Oral) and Carmustine(IV)

- They are lipid soluble and can, therefore, ***cross the BBB***,
- Metabolites secreted in urine.

- Because of their excellent penetration, they can be used against tumours of the brain and meninges.
- Severe cumulative depressive effect on the bone marrow.

C- Alkyl sulfonates

Busulphan

- It has a selective effect on bone marrow and depresses the formation of granulocytes and platelets in low dosages and red cells in higher dosages. In high doses, it produces a rare but sometimes fatal pulmonary fibrosis, ”***busulfan lung***”.
- No effect on lymphoid tissue or the gastrointestinal tract.
- It is used in chronic granulocytic leukemia

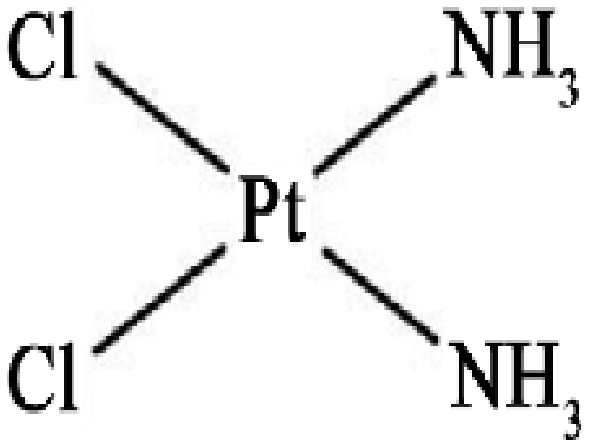
D-Platinum compounds

Cisplastin

- Water soluble complex=central Pt

Actions: similar to alkylating agents

- On entering into cell, Cl- ion dissociate
- Complex reacts with water & then With DNA
- Causes intrastrand cross linking==breaking of H bonds b/w G & C bases ⇒ denaturation of DNA chain



Cisplatin

Cont…

- Cisplastin is given by slow intravenous injection or infusion.
- It is seriously nephrotoxic
- It has low myelotoxicity , very severe nausea and vomiting.
- ***Ondansetron*** (5HT3 antagonist) is effective to reduce to reduce nausea & vomiting
- Tinnitus and hearing loss in the high frequency range, peripheral neuropathies, hyperuricaemia and anaphylactic reactions.

- **Poor penetration into CNS**

Clinical uses (solid tumours) Lung cancer, esophageal esophageal & gastric cancer, head & neck cancer & genitourinary cancers (testicular, ovarian & bladder)

1. Alkylating agents primarily target which component of cancer cells to prevent their growth? (best choice)

a. Cell membrane

b. DNA

c. Ribosomes

d. Mitochondria

2. Which of the following drugs causes hemorrhagic cystitis?

a. Melphalan

b. Chlorambucil

c. Cyclophosphamide

d. Ifosphamide

2. Anti-metabolites

- Structural analogues of naturally occurring metabolites
- **Mode of action:** *Compete with natural metabolites for enzyme systems → inhibition of nucleic acid synthesis*

CCS *(S phase)*; effective against rapidly growing neoplasms

Examples of Anti-metabolite agents

Folic acid antagonists

- *Methotrexate*
- *Pemetrexed*

Purine antagonists

- *Mercaptopurine*
- *Thioguanine*

Pyrimidine antagonists

- *Fluorouracil*
- *Capecitabine (prodrug of 5-FU)*

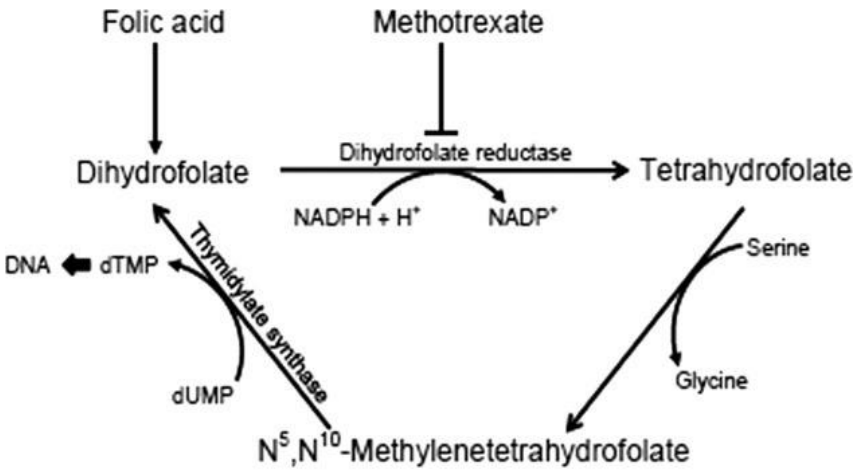
Deoxynucleoside analogues:

- *Cytarabine*
- *Gemcitabine*
- *Fludarabine*
- *Nelarabine*
- *Cladribine*
- *Clofarabine*
- *Pentostatin*

A-Folic acid antagonists

E.g Methotrexate

- The structures of methotrexate and folic acid are similar.
- Folates are essential for the synthesis of purine nucleotides and thymidylate ⇒DNA
- Folate consists of three elements: a ***pteridine ring, p-aminobenzoic acid (PABA) and glutamic acid***
- ***Higher affinity for Dihydrofolate reductase.***



Cont…

- Poor cns penetration
- Given Orally, IV, Intra-thecal.
- Unchanged drug excreted in Urine.

Clinical uses:

- acute lymphoblastic leukemias, Burkitt's lymphoma, in adjuvant therapy of breast carcinoma; in the palliation of metastatic breast, head, neck, cervical, and lung carcinomas

ADR:- depression of the bone marrow, damage to the epithelium of the GIT, pneumonitis.

- At high-dose regimens → nephrotoxicity.

High-dose regimens, must be followed by ***'rescue'*** with ***leucovorin*** (a form of FH4) or folinic acid to treat folic acid deficiency

B-Pyrimidine Antagonists

Fluorouracil

- An analogue of uracil
- It is converted into metabolite fluorodeoxyuridine monophosphate (FDUMP,)
- inhibits thymidylate synthetases and prevents the synthesis of thymidine
- Fluorouracil is usually given parenterally.

Clinical uses:- combination regimens in the treatment of breast cancer, palliative treatment of gastrointestinal adenocarcinomas.

1. **ADR**:- GIT epithelial damage, myelotoxicity, hand-foot syndrome.

- Crosses BBB

DNA Analogues

e.G Cytarabine

- Cytosine arabinoside.
- Analogue of 2'deoxy cytidine
- Cytarabine enters the target cell and undergoes phosphorylation reactions to give the cytosine arabinoside trisphosphate→↓DNA polymerase by its triphosphate.
- Poor CNS penetration
- Given IV and Intrathecal

Clinical uses:-is used in the chemotherapy of acute myelogenous leukemia, it has been used intrathecally in the treatment of meningeal leukemias and lymphomas as an alternative to methotrexate.

ADR:- GIT epithelial damage , myelotoxicity , nausea and vomiting.

Purine Antagosists

E.G 6-mercaptopurine, Azathioprine

- Mercaptopurine is used in the maintenance therapy of acute lymphoblastic leukemia.
- Metabolised by Xanthine oxidase

3. Cytotoxic Antibiotics

- includes the Anthracyclines *(e.g. doxorubicin, daunorubicin, epirubicin, mitoxantrone, etc*) and other drugs such as: *Actinomycin-D, Bleomycin, Plicamycin, Adriamycin and Mitomycin*.

- **Various modes of action:**
  - *Intercalate DNA → inhibition of DNA synthesis*
  - *Generate highly reactive free redicals*
  - *Inhibit vital enzymes in cell cycle e.g. Topoisomerase*

Cont…

Doxorubicin

anthracycline has several cytotoxic actions.

- It binds to DNA and inhibits both DNA and RNA synthesis.
- Its main cytotoxic action is mediated through an effect on topoisomerase II (a DNA gyrase).

- Doxorubicin interacts with molecular oxygen producing superoxide ions and hydrogen peroxide , which cause single strand breakages in DNA.
- Binds cell membrane & alter fluidity & ion transport

PK=

- IV route
- Metabolized extensively
- Doxorubicin can cause cumulative, **dose-related cardiac damage**, leading to dysrhethmias and heart failure.
- Ameliorated by **Dexrazoxane**
- Poor CNS penetration
- Metabolites and Unchanged drug in Bile and Urine

- Extravasation → ***local tissue necrosis***.
- Marked hair loss

Clinical uses:- carcinomas of the breast, ovary, endometrium, bladder, and thyroid,

it is included in several combination regimens for lymphomas and Hodgkin's disease.

Bleomycin

- The bleomycins are a group of metal- chelating glycopeptide antibiotics that degrade preformed DNA, causing chain fragmentation and release of free bases.
- most effective in the G2 phase of the cell cycle and mitosis, also active against non-dividing cells
- Causes little myelosuppression

Clinical uses:- Advanced testicular carcinomas, Hodgkin's and non-Hodgkin's lymphomas.

ADR= Its most serious toxic effect is ***pulmonary fibrosis***. Allergic reactions . Mucocutaneous reactions and may develop hyperpyrexia.

4. Natural Anticancer Agents

Plant alkaloid derivatives:

- Camptothecins (e.g. ***Topotecan***),
- Podophyllotoxin (e.g. ***Etoposide***)
- Taxanes (e.g. ***Paclitaxel***), and
- Vinca alkaloids *(e.g.* ***Vincristine, Vinblastine****).*

Camptothecins (e.g. Topotecan)

- *Also called DNA topoisomerase I inhibitors*
- inhibit topoisomerase enzyme required for DNA replication and repair;
- Used in several types of cancers: e.g. colorectal, lung, ovarian cancers, etc
- Dose-limiting toxicity: myelosuppression

Podophyllotoxins (e.g. *Etoposide, Teniposide, Podophyllin, etc*)

- Act mainly in the G2 phase of cell cycle → prevent mitosis –*inhibit topoisomerase II*
- Clinical Uses:
  - *Etoposide used mainly to treat testicular and small cell lung cancer;*
  - *Teniposide used mainly for childhood acute lymphocytic leukemia*
  - *Podophyllin used topically for localized plantar warts*

- Dose-limiting toxicity: myelosuppression

Taxanes (e.g. Paclitaxel, etc)

- Antimitotic agents → inhibit cell division
- Stabilises Mitotic spindles.
- Used mainly for advanced breast and ovarian cancers

- Dose-limiting toxicity: neutropenia

Vinca alkaloids

(e.g. Vincrinstine, Vinblastine, Vinorelbine)

- CCS agents: Inhibit mitotic spindle formation → stops mitosis;
- Drugs have similar structures but different antineoplastic activity and adverse effect profiles

Clinical Uses:

- Vincristine: Hodgkin's disease, Acute lymphoblastic leukemia, and non-Hodgkin's lymphomas;
- Vinblastine: Hodgkin's disease and choriocarcinoma
- Vinorelbine: Non–small cell lung cancer

Common A/E:

- Tissue damage with extravasation *(leaking of medication into soft tissues around venipuncture site)*
- Bone marrow depression
- Peripheral neurotoxicity

5. Monoclonal Antibodies

- Inhibit tumour growth by combining with growth factor receptors on malignant cell surfaces;
- Used in conjunction with other agents

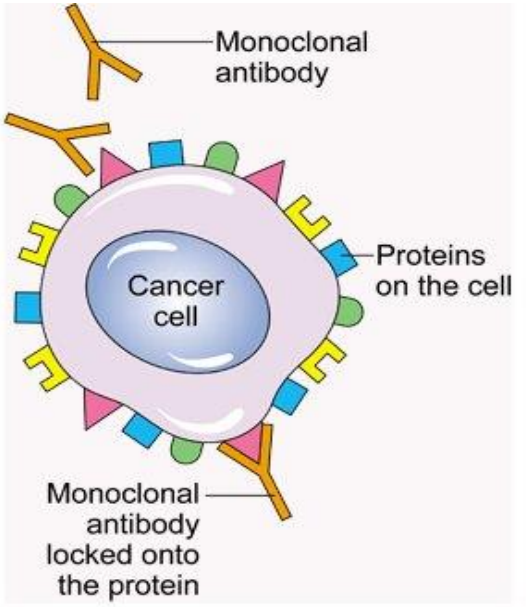


Diagram showing a monoclonal antibody attached to a cancer cell
© CancerHelp UK

Clinical Uses:

- ***Trastuzumab*** used in breast cancer *(targets HER2 receptors)*
- ***Alemtuzumab, Ibritumomab, Gemtuzumab, and Rituximab*** used in lymphocytic leukemia & non-Hodgkins lymphoma
- ***Gemtuzumab*** used in treat acute myeloid leukemia

Adverse effects: Allergic rxns, CVS toxicity, blood dyscrasias

6. Hormones & Hormone Inhibitors

Used to suppress hormone-dependent tumor growth

- **Adrenal Corticosteroids -** used in acute lymphocytic leukemia and lymphomas
- **Testesterone** - used in breast cancer
- **Estrogen -** used in prostate cancer
- **Anti-Estrogen drugs e.g. *Tamoxifen, Anastrozole*** - used in estrogen-dependent (pre-menopausal) breast cancer
- **Anti-Androgens e.g. Flutemide** - used in prostate cancer
- **GnRH analogues e.g. Leuprolide** - used in prostate cancer
- **Progestins** - used in endometrial carcinoma

7. Miscellaneous Cytotoxic Agents

- **L-*Asparaginase*** - an enzyme that inhibits cellular protein synthesis and reproduction by depriving cells of required amino acids. Used in acute lymphocytic leukemia
- ***Hydroxyurea*** - acts in S phase to impair DNA synthesis. Used in leukemia, melanoma, and advanced ovarian cancer
- ***Procarbazine*** - inhibits DNA, RNA & protein synthesis. Also a MAOI. Used in Hodgkin's disease
- ***Interferon-alfa*** - used to treat hairy cell leukemia, chronic myelogenous leukemia, Kaposi's sarcoma, etc
- ***Imatinib*** - tyrosine kinase inhibitor; inhibits cell proliferation and increases apoptosis in chronic myelogenous leukemia

- Questions

3. Which of the following drugs are alkylating agents?

a. Vincristine
b. Doxorubicine
c. Cyclophosphomide
d. Cisplatin

2.Which of the following drugs are cell cycle specific ?

a. Vincristine
b. Cisplatin
c. Doxorubicine
d. Cyclophosphamide

3. Hemorrhagic cystitis is a side effect of:

a. Carmustine
b. Doxorubicine
c. Cyclophosphomide
d. Paclitaxel

4. Which of the following is used to prevent hemorrhagic cystitis :

a. Acrolein
b. Mesna
c. Allupurinal
d. None of the above

General Adverse effects of Cytotoxic Drugs

- **Bone marrow depression:** - Anemia, Leucopenia, thrombocytopenia or pancytopenia.
- **Immunosupression & myelosuppression:** - increase liability to infection and delayed healing of wounds, etc
- **GIT disturbances:** - Typhlitis, Nausea, vomiting and GIT ulcers
- **Alopecia (Hair loss);**
- **Gonadal damage**: - Infertility, Sterility, Amenorrhea and Azospermia
- **Teratogenicity and Mutagenicity**
- **Secondary malignancy** (secondary neoplasia)
- **Tumor Lysis Syndrome** → Hyperuricemia, electrolyte elevation → renal failure, cardiac arrhythmia, etc
- **Organ damage:** Hepatotoxicity, Nephrotoxicity, Cardiotoxicity, Ototoxocity, etc (due to toxic free radicals)

Cytoprotectant Agents

Cytoprotectants reduce severe adverse effects of cytotoxic drugs;

- **Amifostine:** ameliorates cisplatin-induced renal damage;
- **Dexrazoxane:** decreases cardiac toxicity of doxorubicin;
- **Colony-stimulating factors (e.g. Erythropoietin, filgrastim, oprelvekin, and sargramostim):** stimulate bone marrow erythropoiesis;
- **Leucovorin:** used with high-dose Methotrexate;
- **Mesna:** decreases cyclophosphamide-induced cystitis;

COMBINATION THERAPY IN MALIGNANT DISORDERS

Rationale:

- Synergism: - *Each drug attacks cancerous cells at different phases of cell cycle;*
- Decrease incidence of resistance;
- Decrease incidence of adverse effects
- Optimise doses

End of Session.....

Further Reading

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