ANTICANCER DRUGS

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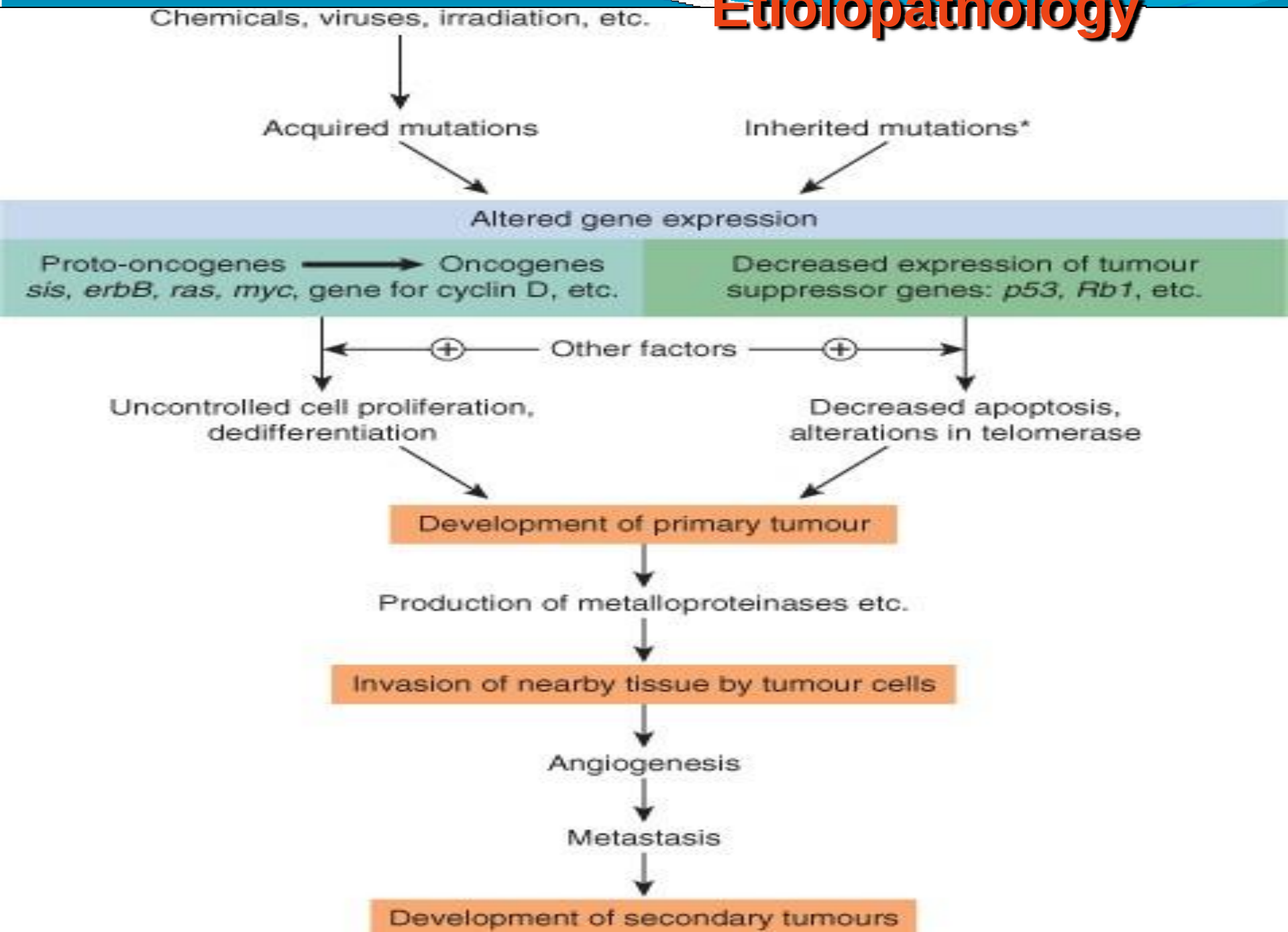
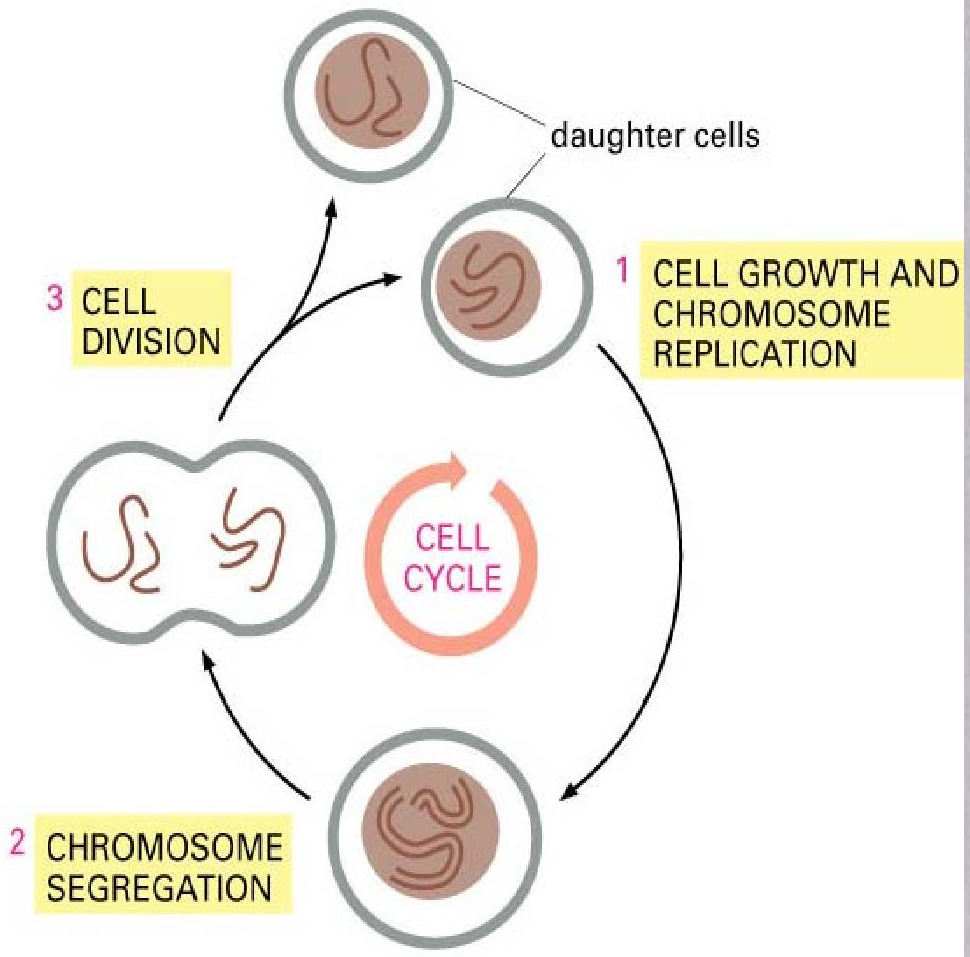
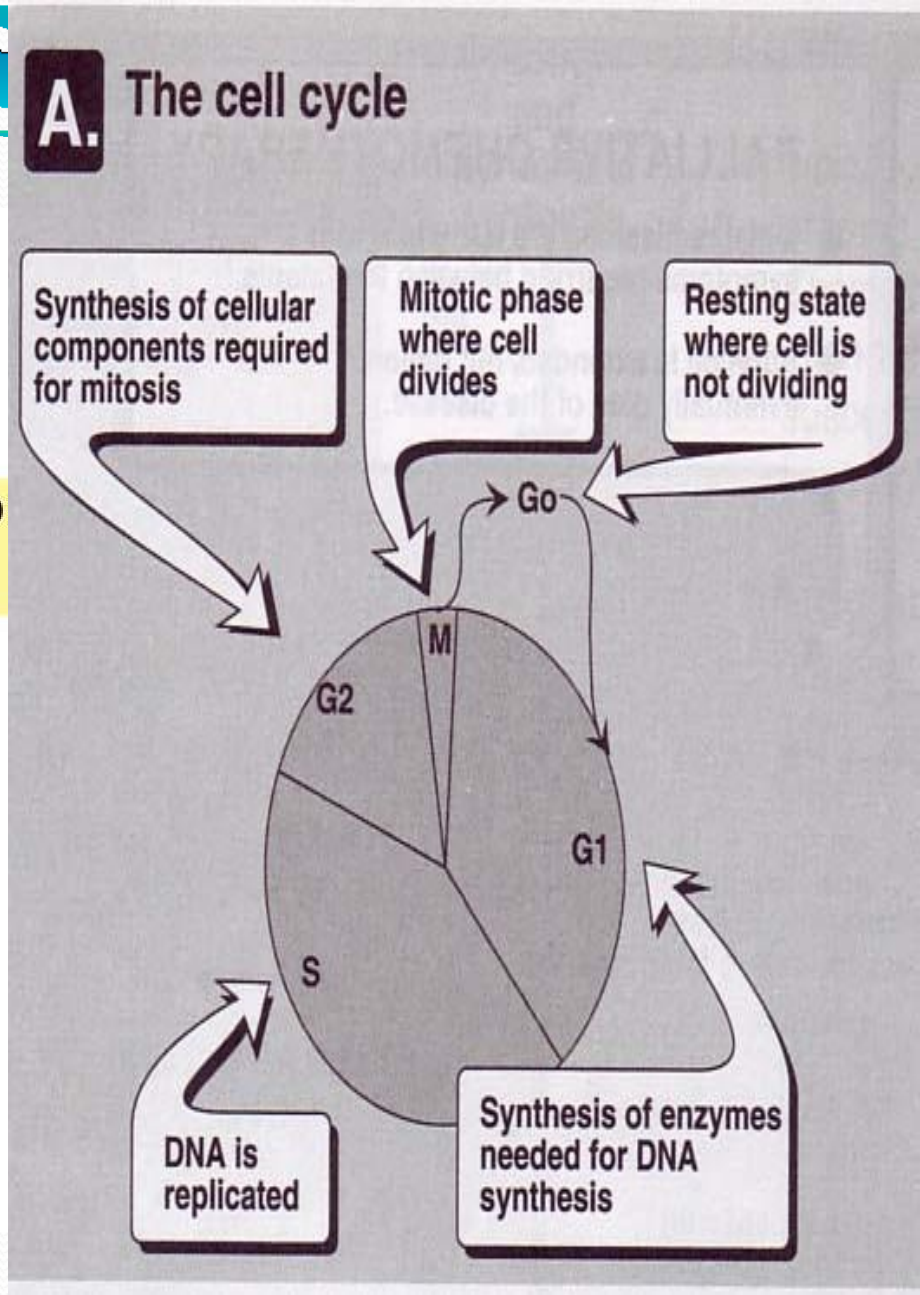
Etiolopathology



Cell Cycle = Growth, Division

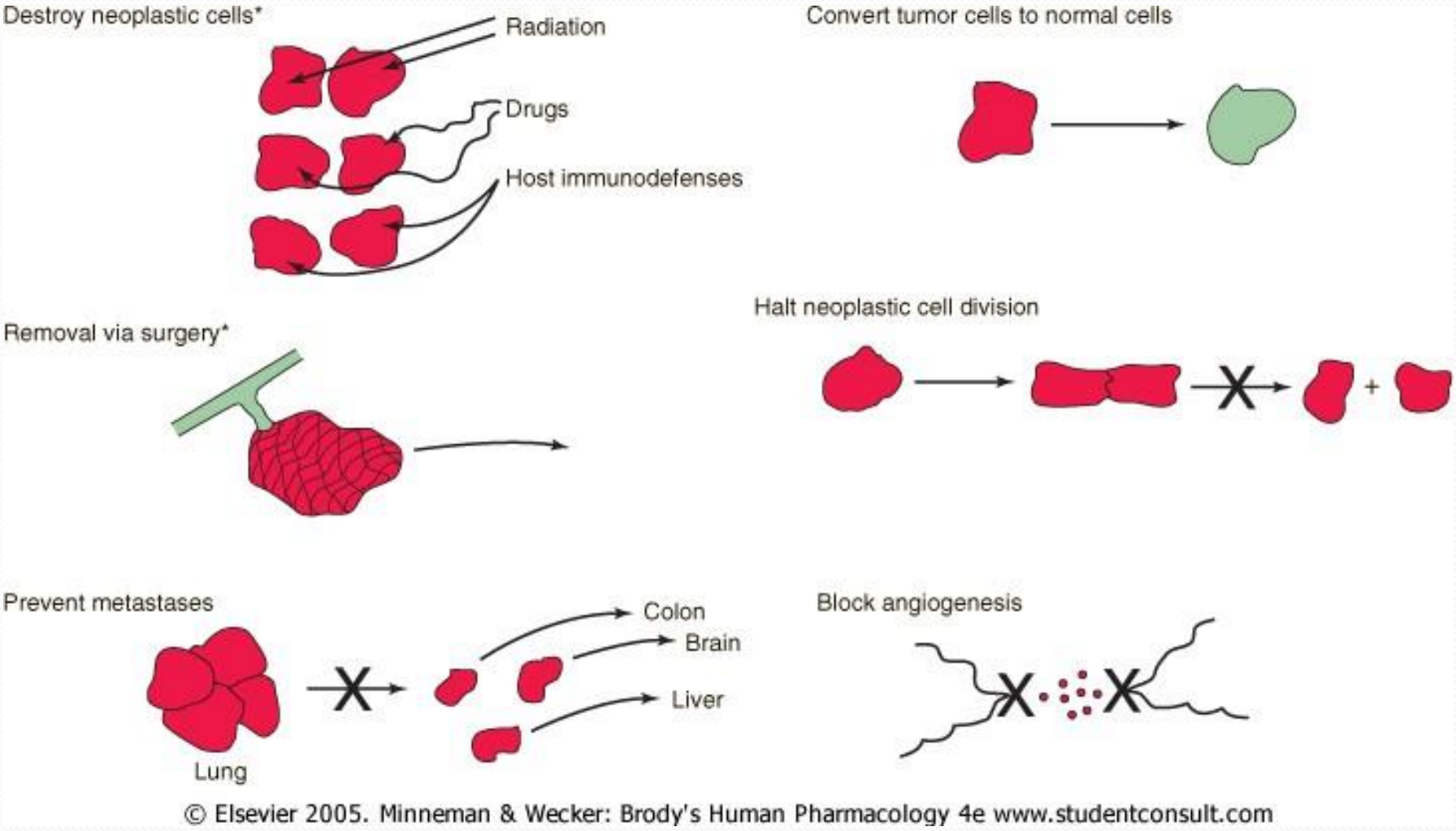




Characteristics of Cancer Cells

- The problem:
  - Cancer cells divide rapidly (cell cycle is accelerated)
  - They are “immortal”
  - Cell-cell communication is altered
  - uncontrolled proliferation
  - invasiveness
  - Ability to metastasise

Major approaches to therapy of cancers



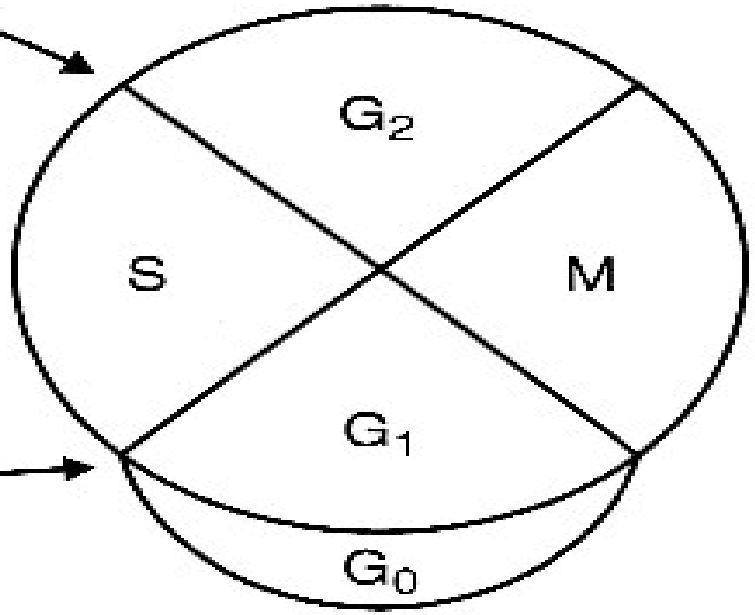
CLASSIFICATION

- Alkylating agents -
  - nitrogen mustards- Mechlorethamine , Cyclophosphamide,Chlorambucil
  - Ethylenimines – Thio-tepa
  - Alkyl sulfonate – Busulfan
  - Nitrosoureas - Carmustin , Streptazocin
  - Triazine – Dacarbazine
- Antimetabolites -
  - Folate antagonist - Methotrexate
  - Purine antagonist- 6-mercaptopurine thioguanine, Azathioprine pentostatin
  - Pyrimidine antagonist- 5-Flurouracil , Floxuridine
- Antibiotics – Actinomycin-D , doxorubicin , bleomycin
- Epipodophyllotoxins – Etoposide , teniposide
- Camptothecins – Topothecan , Irinotecan
- Taxanes – Paclitaxel , docetaxel
- Vinca alkaloids – Vincristine , Vinblastine , Vinorelbine

- Miscellaneous - Procarbazine, Mitotane , L-asparginase, Cisplatin,interferons alpha

- Hormones and their antagonists - Glucocorticoids, Androgens , antiandrogens , estrogens , antiestrogens, Progestins , Aromatase inhibitors

Cell Cycle Specific (CCS) & Cell Cycle Non-Specific Agents (CCNS)



G_2 phase
bleomycin
etoposide

S phase specific
cytarabine
6-mercaptopurine
6-thioguanine
methotrexate
hydroxyurea

M phase
vinblastine
vincristine
pacilitaxel

G_0 phase
alkylating agents
antitumor antibiotics
nitrosoureas
dacarbazide
cisplatin

Alkylating agents

MOA

- Alkylate within DNA at the N7 position of guanine resulting in cross linking of DNA which leads to ring clevage

Toxicity

- Bone marrow depression, with leukopenia and thrombocytopenia

  Cyclophosamide cause hemorrhagic cystitis reduced by co administration with MESNA

Therapeutic uses

- Used to treat a wide variety of hematologic and solid tumors

Thio-TEPA – ovarian cancer
Busulfan – chronic myeloid leukemia
Nitrosoureas - brain tumors
Streptozotocin – insulin-secreting islet cell carcinoma of the pancreas

Anti metabolites

Folate antagonists

- Folate is an essential dietary factor, from which THF cofactors are formed which provide single carbon groups for the synthesis of precursors of DNA and RNA
- To function as a cofactor folate must be reduced by Dihydrofolate reductase (DHFR) to Tetrahydro folate (THF)

MOA

- The enzyme DHFR is the 1º site of action
- Methotrexate prevents the formation of THF, causing an intracellular deficiency of folate coenzymes and accumulation of the toxic inhibitory substrate, DHF finally interrupting DNA and RNA synthesis

Therapeutic uses

Methotrexate- psoriasis, rheumatoid arthritis, acute lymphoblastic leukemia, meningeal leukemia, choriocarcinoma, osteosarcoma, mycosis fungoides, Burkitt's and non-Hodgkin's lymphomas, cancers of the breast, head and neck, ovary, and bladder

Toxicity -Bone marrow suppression

(Rescue with leucovorin (folinic acid))

Nephrotoxic

(give sodium bicarbonate to alkalinize the urine)

Purine antagonist

MOA- it will incorporate in to DNA and leads to breakdown of the DNA strand also cause ↓se DNA synthesis

Mercaptopurine/thioguanine

- Must metabolized by HGPRT to the nucleotide form
- This form inhibits numerous enzymes of purine nucleotide interconversion

PYRIMIDINE ANTAGONIST

MOA

- 5-FU inhibits thymidylate synthase therefore causing depletion of Thymidylate
- 5-FU is incorporated into DNA
- 5-FU inhibits RNA processing

Therapeutic uses

- Metastatic carcinomas of the breast and the GI tract
- hepatoma
- carcinomas of the ovary, cervix, urinary bladder, prostate, pancreas, and oropharyngeal areas
- Combined with levamisole for Tx of colon cancer

Cytarabine

Therapeutic uses

- Induction of remissions in acute leukemia
- Treats meningeal leukemia
- Treatment of acute nonlymphocytic leukemia
- In combination with anthracyclines or mitoxantrone it can treat non-Hodgkin's lymphomas

Toxicity

- Nausea
- acute myelosuppression
- stomatitis
- alopecia

Vinca alkaloids

- Vincrystin and vinblastin are obtained from *Vinca rosea* (periwinkle plant)
- MOA – They bind to the microtubules in mitotic apparatus and arrest cell division in metaphase
- Vincrystin – Toxicity is neurotoxic , bone marrow depression

  uses- leukaemias, Hodgkin's lymphoma , wilms tumor and brain tumor
- Vinblastin- causes bone marrow depression, alopecia and vomiting and used with Bleomycin and Cisplatin in testicular tumors and also in Hodgkin's lymphoma

Podophyllotoxins(MOA)

- Blocks cells in the late S-G_2 phase of the cell cycle through inhibition of topoisomerase II
- Resulting in DNA damage through strand breakage induced by the formation of a ternary complex of drug, DNA, and enzyme
- Antibiotics (MOA)- High-affinity binding to DNA through intercalation, resulting in blockade of DNA and RNA synthesis
- Dactinomycin is used in wilms tumor rhabdomyosarcoma and choriocarcinoma
- Daunorubicin, Doxorubicin is used in acute leukaemias
- Bleomycin is obtained from the *streptomyces verticillus* it forms free radicles and cause breakage of DNA . It is used in solid tumors , testicular tumors etc
- Taxanes(MAO)- it binds to the β-tubulin of microtubules and arrest mitosis

Hormone antagonist

- Formestane, Anastrazole – inhibits the aromatase enzyme
- Aminoglutethimide- inhibits the corticosteroid synthesis
- Tamoxifen – blocks estrogen receptors
- Radio active isotopes

Radio isotope	action and use
Radio phosphorous(P32)	Emits β rays and useful in bone cancer treatment
Strontium chloride	Emits β rays and useful to alleviate pain in painful bony metastases
Radio active iodine(I131)	Used in treatment of thyroid cancer

Miscellaneous drugs

- L-asparaginase – it is an enzyme which converts asparagine to aspartic acid . normal cells can synthesize it, cancer cell have to depend on host cell
- Cisplatin – inhibits DNA synthesis . Toxic effects are ototoxicity , nephrotoxicity , anemia , nausea , vomiting
- Uses - useful in ovarian and testicular tumors

Other agents

- Interferons like interferon α are used in hairy cell leukaemia
- Monoclonal antibodies are immunoglobulins that react specially with antigens present on cancer cells . Allergic reactions are common . Rituximab attaches to B cells causing lysis of this cells
- Haemopoetic growth factors like erythropoietin and myeloid growth factors and thrombopoietin are used to treat bone marrow supression

Choice of drugs in some malignancies

malignancy	preferred drugs
Acute lymphatic leukaemia	Vincristine + prednisolone
Chronic lymphatic leukaemia	chlorambucil + prednisolone
Hodgkin's disease	vinblastin + doxorubicin + dacarbazine + bleomycin
Non-Hodgkin's lymphoma	Cyclophosphamide + doxorubicin + vincristin + prednisolone
Carcinoma of stomach	Fluorouracil + cisplatin
Carcinoma of head and neck	Fluorouracil + Cisplatin
Carcinoma of lung	Cisplatin + paclitaxel

General problems with anticancer drugs

- Most of them are antiproliferative, i.e. they damage DNA and so initiate apoptosis.
- They also affect rapidly dividing normal cells.
- This leads to toxicity which are usually severe.
- To greater or lesser extent the following toxicities are exhibits by all anticancer drugs.

Adverse Reactions of Antineoplastic Drugs in Humans

Tissue	Undesirable Effects
Bone marrow	Leukopenia and resulting infections
	Immunosuppression
	Thrombocytopenia
	Anemia
GI tract	Oral or intestinal ulceration
	Diarrhea
Hair follicles	Alopecia
Gonads	Menstrual irregularities, including premature
	menarche; impaired spermatogenesis
Wounds	Impaired healing
Fetus	Teratogenesis (especially during first trimester)