Anti Cancer.

- problem with cancer? too many cells.
- solution: kill of those cells.
  ↓
  give cytotoxic drugs.
  ↓
  But they are non-specific.
  ↓
  target some unique ppty of cancer cells and make drugs against that
  ↓
  targetted chemotherapy.
  ↓
  ppty we are targetting: rapid division.

- But problem faced: there are other rapidly dividing cells of own body too.

lot of cells die
↓
reduce lot of purine/proteins
↓
X combine.
↓
↓ uric acid

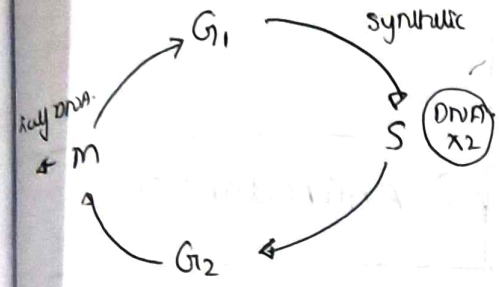
- S/E of anticancer drug will be due to drug affection other rapidly dividing cells.

Rapidly dividing cells

1. Bone marrow → B.M supression. anemia, Leucopenia, Thrombocytopenia.
2. Hair cells → Alopecia.
3. GIT → mucositis → Diarrhoea.
4. Nausea, vomiting.
5. Uric acid → hyperuricemia.

general S/E of all anticancer drugs

Cell cycle.



- at end of S phase, DNA doubles, that is, DNA synthesis occurs in this phase.

① drugs that inhibit formation of DNA
↓
S phase specific.

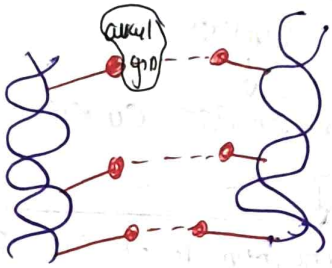
② Drugs that stop mitosis
↓
M phase specific

③ Drugs that bind to DNA
↓
on all phases
↓
Non-specific.

Classification of Anticancer drugs Based on Mechanism of Action.

① Alkylating Agents.

- they add alkyl group on DNA.



→ normally, DNA fragments dont interact with each other....
→ But on alkyl addition, they interact, i mean the alkyl group will interact and form Dimers which are not seen normally.
→ abnormal thing is formed
→ Activation of Enzymes
→ Destruction of DNA

DIMERS
↓
① of Enzymes
↓
DNA destroyed.
↓
cell death

- most common site of alkylation
↓
N_7 of Guanine

If - Ifosfamide
Bu - Busulfan
not - Nitrosoureas
Prosent - procarbazine
Tuke - Temozolomide
my - melphalan, mitomycin C.
Cycle - ~~Cyclophosma~~ cyclophosphamide

S/E
④
- Tumical one).
- 2° Leukemia
- Infertility (sterility) Gonadotoxic.

- alkylating agents are non cell cycle specific cause they are binding to DNA.

Cyclophosphamide & Ifosphamide.

Metabolized

- 4 - hydroxycyclophosphamide (Cytoxan)
- Aldesphosphamide. (Ifosphamide)

Anticancer ppty ✓

Good metabolite.

Acrolein (TOXIC)

Inflammation of bladder.

Cystitis.

Hemorrhagic Cystitis.

Cyclophosphamide → only @ high dose cause HC

Ifosphamide → at any dose.

HC : treatment → steroids.

prevention of HC.

MESNA

mercapto ethane sulfonic acid.

- Oral / IV.

Should be given at:

- any dose of Ip
- high dose of cycloph.

Cyclophosphamide also cause pulmonary fibrosis.

Drugs Causing pulmonary fibrosis

- cyclophosphamide (AC)
- Carmustine (AC)
- Busulfan (AC)
- methotrexate (AC)
- Amiodarone. (anti arrhythmic)
- Bleomycin (AC)

- Cyclo
- Car
- Bu
- Bleo
- drone

Blow born

platinum Coordination SKIPPED

(3) Antimetabolites

- Stops DNA formation
- ∴ S phase specific

(a) folic acid.

(b) purines

(c) pyrimidines

Folic acid.

Pteridine + PABA + Glu.

↓ F.A synthase.

DHFA Folic acid. (inactive)

↓ DHFA reductase.

Folinic acid (THFA)

↓

DNA

- Humans - take ready made folic acid.
- Bacteria synthesize FA
- so there is no point in ⊖ of F.A synthase

Folic acid (DHFA)

methotrexate (−) → DHF Reductase

Folinic acid (THFA)

methotrexate

Anticancer.

R.A

↑ Adenosine.

⊖ DHFRase

o S phase Specific

• Toxicity.

: other general ✓

specific :

① megaloblastic anemia

② Hepatotoxicity

③ Pulmonary Fibrosis.

In methotrexate Toxicity, we give

FOLINIC ACID.

or Leucovorin/

Citrovorum.

• there is no point in giving folic acid, as it can't form folinic acid.

USES

Choriocarcinoma DOC

Acute Leukemia (ALL, AML)

Non Hodgkin's lymphoma.

Crohn's disease

Ectopic pregnancy

R.h. arthritis DOC

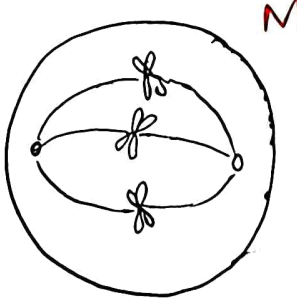
New drugs

• pemetrexed - mesothelioma.

• pralatrexate.
- peripheral T cell lymphoma.

⑥ DRUGS ACTING ON MITOTIC SPINDLE

M phase specific



spindle formation is by polymerization of Tubulin

Tubulin → polymerization

• also, spindle should break to move chromosome to opposite poles.

Drugs are targetted at :

① Tubulin polymerization

② spindle breaking

⊖ formation

• vincristine

• vinblastine

⊖ Breakdown

Paclitaxel.

PACLITAXEL.

Vincristine

↓

Marrow sparing anticancer drug.

Vin, vinblastine

S/E

• Peripheral neuropathy

• SIADH.

New drugs.

ERIBULIN. | Breast Ca.

IXABEPILONE | Breast Ca.

Estramustine | prostate Ca

Cyclophosphamide

INTRO

- cyclophosphamide is an alkylating agent.
- belonging to Nitrogen mustard class.
- It is a prodrug that requires activation
- It has both antitumor & immunosuppressant properties
- active metabolites: by hepatic metabolism.
  1. aldophosphamide
  2. phosphoramide.

ALDOPHOSPHAMIDE
PHOSPHORAMIDE.

MOA

- they form highly reactive intermediates → carbonium ion.
- that transfers alkyl group to DNA by forming covalent bonds.
- most common: N7 of guanine.
- alkylation results in:
  - cross linking
  - abnormal base pairing
  - strand breaking.

→ Inhibit cell division and protein synthesis

CI

- pregnancy
- Severe Bone marrow supression.
- liver, kidney severe disease
- active infection

Nitrogen mustard

- derivative of sulfur mustard gas → used in world war.
- cell cycle non specific action.
- Actions:
  - cytotoxic
  - Immunosupressant
  - Radiomimetic.
  - mutagenic & carcinogenic.

USES

- CHOP regimen – Non-Hodgkin's lymphoma.
- CMF regimen – carcinoma breast
- ovarian cancers / solid tumors in children.
- Autoimmune diseases.

ADR

1. Haemorrhagic Cystitis
   → due to acrolein - toxic metabolite.

prevention: ① Hydration
② MESNA - use.
- conjugate acrolein in urine

Rx: stop drug immediately
- vigorous hydration.
- cystectomy

2. SIADH.
3. Alopecia
4. sterility.
5. teratogenicity
6. Leukemia.

lesser myelosupression & mucosal damage.

Methotrexate.

- mutho brexate?
- folinc acid in overdose?
- folinic acid + 5-fluorouracil?

INTRO

→ Antimetabolite.

→ folic acid antagonists.

- antineoplastic + Immunosupressant

MOA S-phase specific

- Folic acid Antagonist.
- mutholrexcate Enters into cells
  ↓
  utilizing the (folate carrier)

- mutholrexcate
  ↓ folyl poly glutamate synthase. (FPGS)
  polyglutamate form (more active).

- DHFA folic acid
  methotrexate ⊖ DHF Reductase.
  ↓
  THFA
  folinic acid
  - pseudoirreversible inhibition.

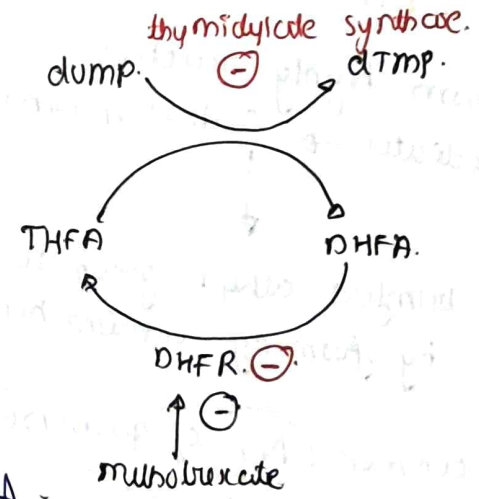
⊖ De novo purine synthesis

- THFA dyficency
  ↓
  ⊖ of DNA, RNA, and protein Synthesis.

⊙ ⊖ thymidylate synthase enzyme.

dump. deoxyuridine monophosphate
⊖ Inhibits thymidylate synthase enzyme.
↓
dTMP.

→ Inhibits DNA synthesis



- S phase specific.

- also inhibit AICAR transformylase.

Mechanism of Resistance

- decreased drug transport
- Reduced formation of active metabolites.
- increased synthesis of DHFR aie.
- altered DHFR aie with reduced affinity for methotrexate.

ACTIONS

- cytotoxic actions.
- Immunosuppressant
- Anti inflammatory.

PK

- orally well absorbed
- 50% plasma protein bound
- Excretion: Renal.
- poor BBB crossing.

Drug Interactions

- salicylates, sulfonamides, Ofloxacin displaces methotrexate from its plasma protein binding site.

- Aspirin, sulfonamides, probenicid etc inhibit renal tubular secretion of methotrexate.
  ↓
  Enhances its toxicity.

ADR

- Bm suppression
- Liver - fibrosis & cirrhosis.
- Pneumonitis, lung fibrosis
- Nausea, vom
- alopecia
- Nephrotoxic: in high dose

LEUCOVORIN RESCUE

- Leucovorin / folinic acid / Citrovorum
- bypass DHFR aie blockade
- reverses toxic effect of methotrexate on normal cells
- cytotoxic effect on cancer cells are maintained.
- Leucovorin is used with high dose of MTX for therapeutic purpose
- also for accidental overdose

USES (UQ)

Neoplastic uses

- choriocarcinoma
- NHL
- ALL in children.
- AML

HDM-L therapy

- High dose methotrexate with Leucovorin rescue.
- 100 times higher dose (25-1000 mg / m² BSA) is infused IV over 6 hours.
  +
- 3-15mg IV calcium Leucovorin
  ↓
- Osteosarcoma
- CNS lymphoma
- childhood ALL

Pemetrexed

- newer congener
- ⊖ thymidylate synthase enzyme.
- ⊖ DHFR aie enzyme
- uses: * mesothelioma.
  * Non-small cell Lung carcinoma.

Non-neoplastic uses

- rheumatic arthritis
- psoriasis
- GVN.

Vinca Alkaloids

- **Source:**
  Catharanthus roseus.
- microtubule damaging agents
- M-phase specific.

→ Vincristine (oncovin)
→ Vinblastine
→ vinorelbine.

MOA (FIGURE)

- Vinca alkaloids ⊖ Tubulin polymerization and assembly of microtubules.

↓

disruption of mitotic spindle.

→ mitosis is inhibited.
→ M phase specific.

PK

- metabolized by CYP450 enzyme
- Bile excretion.

Microtubule damaging agents.

✓ Vinca alkaloids (UQ)

- Vincristine.
- Vinblastine.
- Vinorelbine.

✓ Taxanes. (UQ)

- Paclitaxel
- Docetaxel

USES

Vincristine : Pediatric Leukemia, Lymphomas, Solid tumors.

LIMITED MYELO SUPPRESSIVE ACTION

Vinblastine : Lymphomas, Breast, Testicular Ca Hodgkin's Lymphoma, less neurotoxicity.

Vinorelbine : Semi-Synthetic
Non-Small cell lung Cancer.
Intermediate myelo/Neurotoxicity

ADR

- Vincristine – Neurotoxicity, alopecia, SIADH.
- Vinblastine – B.M Supression. ☆
- Vinorelbine – Neutropenia

C/I

- Neurological disorders that can be worsened.

TAXANES

- Bark of western yew - tree.
- microtubule damaging agents
- M - phase specific.

MoA

- Taxanes binds tubulin subunits and promote assembly
  ↓
  Unusually stable tubulin molecules stacks & fail to depolymerize
  ↓
  chromosomes fail to segregate
  ↓
  cell remains frozen in metaphase.

PK

Paclitaxel - in cremophor emulsion
(Castor oil + alcohol + water)
↓ can cause.
- acute anaphylactoid reactions.

Cremophor emulsion.

ADR

Paclitaxel →
- Glove & stocking Neuropathy
- hypersensitivity reaction (camphor ☺)
- * myelosuppression

Docetaxel →
- Neutropenia*
- Arrhythmia
- Fluid retention

Paclitaxel > Docetaxel.

USES

- Metastatic Ovarian, Breast, Kaposi ✓
- Breast
- Lung
- GI
- Genitourinary
- Head & neck cancers

Head & neck ca. ✓
Small cell lung Ca. ✓

L-asparaginase

Laspargine.
↓
aspartic acid + ammonia

Normal cells →
asparagine synthetase ✓

Lymphoblast cells
No X Asparagine synthetase.
asp deficiency.
Use: (ALL)