Cell cycle →

G_1 – phase → Pre-synthesis interval.

After mitosis some daughter cell pass into a Resting phase or non proliferating phase (G_0).

G_0 phase is the sub phase of G_1.

The point where DNA syn., start known as presynthetic phase G_1.

↗ The DNA syn. occurs in just S phase.

The pre-mitotic or most synthetic phase (G_2). in this phase R.N.A and protein syn. take place.

The mitotic phase in which synthetic activity of the cell is low, (M) chromosome seperate into two daughter cell through sub-phase like as prophase, Metaphase, Anaphase, Telophase.

Phase-dependent drug →

1. drug which act on S-phase → (GMP, GTG) Purine antagonist, methotrexate, FU, (cytosin-arabinosid)/ cytarabine, Hydroxy-urea, Mito-mycin-c, Doxo-rubicin, Daunorubicin.

2. drug which ,, G_1 phase → vinblastin

3. ,, ,, G_2 phase → Daunorubicin, Bleomycin Etopodiac, topotecan

4. drug M phase → vincristin, vinblastin, colchicine, Paclitaxel

(A) Alkylating agent → MOA → Alk., React by forming a Reactive intermediate which contain a positively charge carbonium ione OR Transition complex which forms a co-valent link c̄ negatively charge centre. This Result cross-linking or abnormal base pairing or scission of DNA strand.

These are highly reactive compound formed covalent bond b/w alkyl grp (+ charge) in these molecule and Guanin bases that opposing the strand of DNA.

Adverse eff → Radiomymetic action (X-ray like), carcinogenic, mutagenic, Teritogenic and immunosupressant.

ex →

(1). Cyclophosphamide → Drug interaction → corticosteroid and sex hormone which inhibite the liver microsomal oxidase also, ↓ the action and toxicity of cyclophosphamide

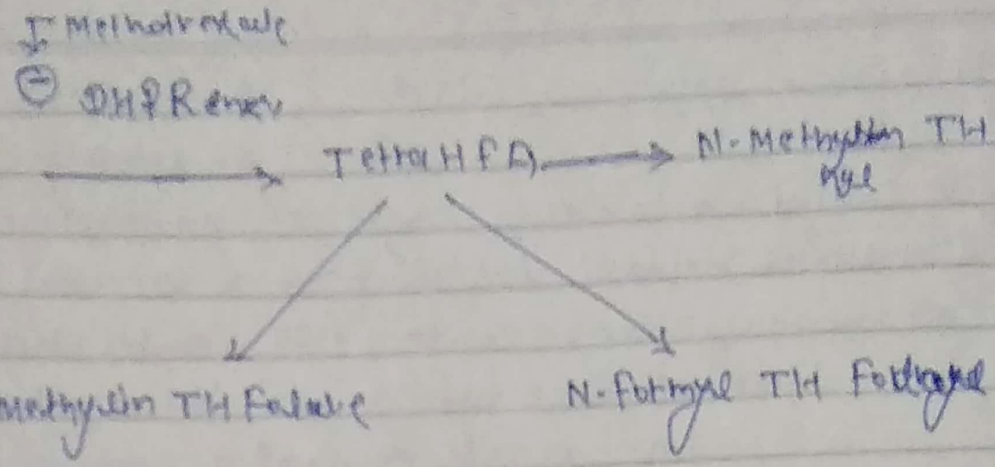
2) Barbiturates which stimulate, ↑ action and toxicity of cyclophosphamide.

(B) Anti-metabolite → ex → Methotrexate → Methotr. enter into cell via and energy dependent, carrier mediated transport syst.

MOA → cell cycle specific - S phase.

→ Methotrexate inhibit DHFR enz - Blocking the conversion of DHFA → Tetra HFA, which is co-Enzyme Required for 1-carbon transfer rxn. in denovo purin synthesis.

Tetra hydrofolate is a co-Enz which depending Enz is formyl transferase.



=> Inhibition of Pnz by Methotrexate is Pseudo-reversible or irreversible type.

Toxicity -> Myelo suppression, Hepatic Fibrosis, Pneumonitis, interstitial pneumonitis, Abortifeciant in first trimester in pregnancy.

Prevention -> Folinic acid (Leucovorin), citrovorum factor and thymidine which counteract the Methotrexate toxicity.

Drug interaction -> Salicylate, Phenyl butazone, sulphonamide, Dicumarol displace it from binding site, ↑ toxicity of methotrexate.

--> Pyrimidine Analogue -> 5FU

MOA -> A fluorinated pyrimidine analogue which converts in to Ribotyde and D-oxyribotyde metabolite (5 fluro 2-deoxy uridine monophosphate) which inhibit thymidylate synthetase Enz and block's the conversion of D-oxy uridilic acid to de-oxy thymidilic acid. and failure of DNA synthesis.

Fluorouracil

↓

5 Fluoro deoxy uridilate

↓ ① inhibition

(Thymidilate synthatase)

② ——————→

uridine Monophosphate → Thymidine Monophosphate.

Toxicity → Bone-marrow depression, Diarrhoea ulceration, Megaloblastic anemia (due to interfere thymidine incorporation into DNA)

ex→ cytarabine → pyrimidine analogue. (cytosine arabinoside) S-phase specific.

MOA → interfere ∈ DNA synthesis by Inhibiting DNA Polymerase.

⇒ cyto metabolite by cytidine-deaminase to uracil arabinocyte.

Adverse effe → Myelo. suppression, Bone marrow depp. Stomachitis.

ex→ Azatabine → It is triacetyl acetyl prodrug of Aza. uridine.

Therapeutic value in Psoriasis.

Mycosis, Fungoids and Polycythemia vera.

(Prodrug)

Purine Analogue → 6MP, 6TG

⇒ Cell cycle specific S-phase.
⇒ An Immunosuppressant.

MOA → they converted in Mono. Ribonucleotide which inhibits the conversion of inosin-mono phosphate to Adenine and Guanine nucleotide also feed back inhibition of D-Novo purine synthesis. 6MP is Metabolised by xanthine-oxidase.

Toxicity → BMD, Reversible jaundice, — Hyperuricemia, (can be Reduce by Allopurinol) → xanthine oxidase-blocker.

(IM)

(C) Vinca-alkaloid → Cell-cycle Specific (Mitotic phase)

MOA → Mitotic inhibitor, bind to Micro-tubular protein (Tubulin) prevents its polymerization and assembly of micro-tubule causes disruption of mitotic spindle and interfere ~~c~~ cyto-skeletal function. thus chromosome Fails to move apart during mitosis (Metaphase arrest occurs) (colchicine like effect)

Toxicity → Vincristine :- Peripheral neuropathy, alopecia,

Vinblastine :- BMD,

) Taxanes → Paclitaxel, Docetaxel.
Taxanes are alkaloidal ester obtain from western yew (Taxus brabifolia)

european yew (Taxus baccata).

MoA → Act as a Mitotic spindle poison, through enhancement of Tubulin polymerization. which is used in advance ovarian cancer, Breast cancer.

↑ An Anti-histamine (H_2 blocker) Recomended to prevent hypersensitivity rxn.

Toxicity → Pneutropenia, Thrombocytopenia. cardiac conduction defect, Alopecia Muscle pain, Myelo suppression.

(E) Etoposide → Plant glycoside :- it is not a mitotic inhibitor but arrest cell in G_2 phase and caused DNA break by effecting topoisomarase-II.

(F) Camptothecin Analogue → Topotican, irinotican these analogues are topoisomarse-I inhibitor. they damage DNA during Replication, act in S. phase and arrest cell. cycle at G_2 phase.

irinotican → it is a prodution & is decarboxylated in liver :- shows cholinergic effect, because it inhibit acetyl cholin esterase enz. (Neutropenia, Thrombocytopenia
Toxicity → Haemorrhigia.

Toxicity (Topotican) → anorexia, diarrhoea,

L-Asparginase → Derived from cultures either E.coli or Arbania carotovora

MOA → it inhibits Asparagine synthetase which catalyses the hydrolysis of Asparagine to Aspartic acid and Amonia. Thus Asparagine depleting action of Asparginase interfere c̄ protein, DNA and RNA synthesis and tumor cell.

⇒ post mytotic (act on (G_1) phase)

Adverse effe → Hypersensitivity, immunosupressant, Neurotoxic, hepato toxic, Hyperglycemia (due to ↓ insulin production)

Doxo-rubicin, Dauno-rubicin → Anthra-cyclin glucoside antibiotic.

they have been isolated from Streptomysis peucetious variety caesious.

MOA → Anthra-cyclin, Intercalate b/w nucleotide pairs and Amino sugars, bind tightly to DNA and block DNA directive R.N.A synthesis and transcription.

⇒ These are phase non specific, activates topoisomerase-II and generate quinon free Radical.

Toxicity → Both cardio toxicity - supra ventricular Tachycardia, Miocardial damage

Daunorubicine → it show maximum action at S phase but toxicity exerted in G_2 phase.

Bleomycine → Glycopeptide produce by Streptomysis verticellus.

cell cycle specific G_2 and M phase.

MOA → cission of DNA strand and interfare c̄ DNA polymerase causing dammage of DNA.

Q/ Mitoxantron → Recently introduce, analogue of Doxo-rubicin c̄ lower cardio toxicity. b/c doesnot produce quinon type free-Radicle.

Toxicity → B.M.D, Mucosal inflamation

Mitomycin-C → isolated from Streptomysis caespitosus same. it is alkylating agent MOA.

Kill cells in G_1-M phase.

Hydroxy-urea → it inhibit ribonucleoside diphosphate Reductase enz, c̄ convert Ribonucleotide to deoxy ribonucletide.

destroy of DNA syn.

Mithramycin → it is chromo-mycin antibiotic. isolated from Streptomysis plecatus.

MOA → inhibit DNA dependent syn of RNA. phase specific for S phase.

Dactinomycin (Actinomycin-D) → isolated from Streptomysis parvulus

M.A → binds to DNA and inhibit RNA syn., Including the syn of Ribosomal R.N.A in the nucleolus.

· at G_1 phase.

(Post Mitotic)

Me Example	Resistence Mechanism of action
Methatrexate, Dalmorubicin	Reduce uptake of drug
cytosin arcubinoside 5-fu	Ab. of Enz to activate drug.
6MP	↑ drug detoxification
Methatrexate	↑ conc. of target Enz
Asparginase	↓ Requirment for specific Metabolic product.
Anti-Metabolite	↑ utalization of alternative pathway
Hormone	↓ no of receptor for a drug.