Unit 4
Chemotherapy of Parasitic Infections

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Chemotherapy of Parasitic Infections

Chemotherapy of Parasitic Infections include the infections caused by parasites.

Examples:

- Tuberculosis
- Leprosy
- Malaria
- Fungal Infection

Antitubercular drugs:

Tuberculosis - most important communicable disease in the world.

Mycobacteria are intrinsically resistant to most antibiotics

-Grows more slowly than other bacteria – antibiotics active against rapidly growing cells

– lipid-rich mycobacterial cell wall is impermeable to many agents

– It grows inside macrophage – poorly penetrated by drugs

– Excellent ability to develop resistance – Multiple Drug Resistant (MDR)

- Combinations of two or more drugs

– to overcome these obstacles

– to prevent emergence of resistance during the course of therapy

The response of mycobacterial infections to chemotherapy is slow - treatment must be administered for months to years, depending on which drugs are used

Classification

According to clinical utility the anti TB drugs can be divided into 2 groups,

First Line : high antitubercular efficacy as well as low toxicity – routinely used.

H-Isoniazid

R-Rifampin

Z-Pyrazinamide

E-Ethambutol

S-Streptomycin

Second Line:

Paraminosalicylic Acid, Cycloserine, Kanamycin, Amikacin, Ciprofloxacin, Olfloxacin, Clarithromycin, Azithromycin

ISONIAZID

- Most active drug for the treatment of tuberculosis
- freely soluble in water
- bactericidal for actively growing tubercle bacilli
- less effective against atypical mycobacterial species

MOA:

- The primary mechanism of action of INH is inhibition of synthesis of *mycolic acids which* are unique fatty acid components of mycobacterial cell wall.

Resistance:

Its prodrug – activated by enzyme catalase-peroxidase – Mutation causes inhibition of this enzyme

Pharmacokinetics

- Readily absorbed from the gastrointestinal tract - diffuses readily into all body fluids and tissues.
- Acetylation by liver N -acetyltransferase, is genetically determined

half-lives :1 hour(fast :1 hour(fast acetylators acetylators) and 3 hours (slow acetylators)

- Excreted, mainly in the urine - need not be adjusted in renal failure

Contraindicated - severe preexisting hepatic insufficiency

Adverse Reactions:

Immunologic Reactions

Direct Toxicity

RIFAMPIN

- obtained from *Streptomyces mediterranei*. Rifampin is bactericidal to *M. tuberculosis and* many other gram-positive and gram-negative bacteria like *Staph. aureus*, *N. meningitidis*, *H. influenzae*, *E. coli*, *Klebsiella*, *Pseudomonas*, *Proteus and Legionella*. *Against TB bacilli*, *it* is as efficacious as INH and better than all other drugs.

MOA:

- Rifampin interrupts RNA synthesis by binding to β subunit of mycobacterial DNA-dependent RNA polymerase (encoded by *rpoB gene and* blocking its polymerizing function. The basis of selective toxicity is that mammalian RNA polymerase does not avidly bind rifampin.

- **Resistance:**

  Mutations result in reduced binding of rifampin to RNA polymerase

Pharmacokinetics:

- It is well absorbed orally, (bioavailability is ~ 70%), but food decreases absorption; rifampin is to be taken in empty stomach. It is widely distributed in the body: penetrates intracellularly, enters tubercular cavities, caseous masses and placenta. Though it crosses meninges, it is largely pumped out from CNS by P-glycoprotein. It is metabolized in liver to an active deacetylated metabolite which is excreted mainly in bile, some in urine also.

Adverse effects:

- The incidence of adverse effects is similar to INH.
- **Uses:** Leprosy, Prophylaxis of *Meningococcal and H. influenzae*

ETHAMBUTOL

- Ethambutol is selectively tuberculostatic and is active against MAC as well as some other mycobacteria, but not other types of bacteria.

MOA:

Inhibits mycobacterial arabinosyl transferases - an essential component of the mycobacterial cell wall.

Resistance:– due to alteration in target gene

Streptomycin (S)

- It was the first clinically useful antitubercular drug. It is tuberculocidal, but less effective than INH or rifampin; acts only on extracellular bacilli.

MOA: Irreversible inhibitors of protein synthesis

Inside the cell, aminoglycosides bind to specific 30S-subunit ribosomal proteins and inhibits protein synthesis

Resistance:

– Inactivation by adenylylation, acetylation, or phosphorylation

Pharmacokinetics:

absorbed very poorly from the intact gastrointestinal tract

intramuscular injection or usually administered intravenously as a 30- to 60- minute infusion

Normal half-life - 2–3 hours, but in renal failure patient it reduces to 24-48 hrs

Adverse effect:

- Ototoxic and nephrotoxic
- Vertigo and hearing loss - common adverse effects and may be permanent
- Dose-related, and the risk is increased in the elderly
- Therapy should be limited - no more than 6 months whenever possible

Para-aminosalicyclic Acid

structural analogue of paminobenzoic acid (PABA)

highly specific for M. tuberculosis - not effective against other mycobacterium species

Combined with isoniazid - an alternative substrate and block hepatic acetylation of isoniazid- increasing Combined with isoniazid - an alternative substrate and block hepatic acetylation of isoniazid- increasing free isoniazid levels.

limited to the treatment of MDR tuberculosis

Ethionamide

Chemically related to isoniazid

Blocks the synthesis of mycolic acids

Poorly water soluble and available only in oral form

Dosage of 15 mg/kg/d - initial dose of 250 mg once daily, which is increased in 250-mg increments to the recommended dosage

Intense gastric irritation and neurologic symptoms as well as hepatotoxic

Capreomycin

peptide protein synthesis inhibitor antibiotic obtained from Streptomyces capreolus

Daily injection of 15 mg/kg/d intramuscularly

treatment of drug-resistant tuberculosis

Strains of M tuberculosis that are resistant to streptomycin or amikacin - susceptible to capreomycin

Nephrotoxic and ototoxic - Tinnitus, deafness, and vestibular disturbances occur

local pain, and sterile abscesses may occur

Cycloserine

inhibitor of cell wall synthesis

0.5–1 g/d in two divided oral doses

Cleared renally - Dose is reduced to half in case of renal dysfunction

peripheral neuropathy and central nervous system dysfunction, including depression and psychotic reactions.

Pyridoxine, 150 mg/d given in addition to it

Kanamycin & Amikacin

Treatment of tuberculosis suspected or known to be caused by streptomycin-resistant or multidrug- resistant strains

Kanamycin is more toxic comparatively – absolute

Prevalence of Prevalence of amikacin amikacin-resistant strains resistant strains is low (< 5%) is low (< 5%)

Also active against atypical mycobacteria

15 mg/kg intravenous infusion

No cross-resistance between streptomycin and amikacin but it occurs with kanamycin

used in combination with at least one and preferably two or three other drugs

Anti Malarial Drugs:

Plasmodium species which infect humans:

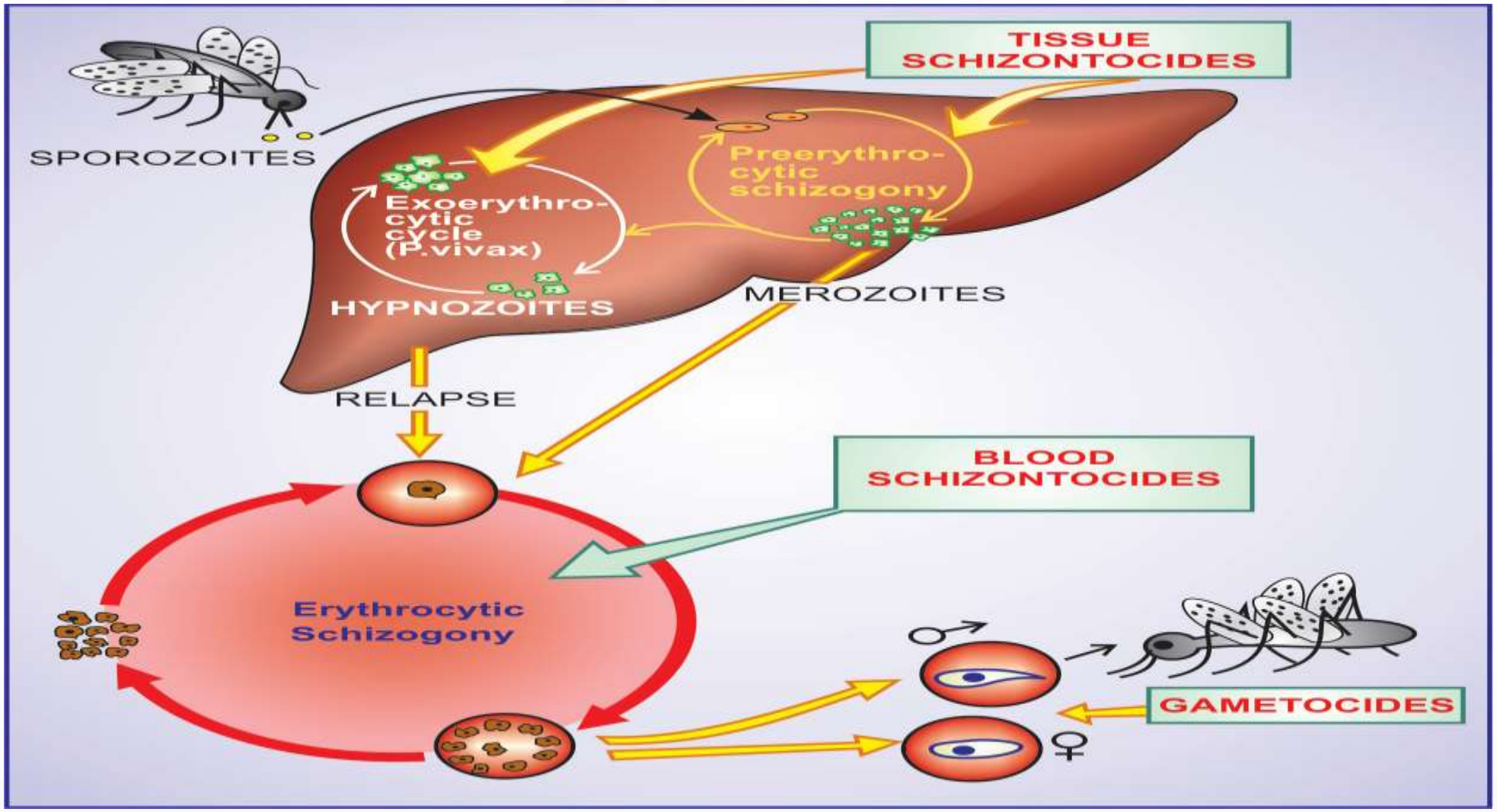
Plasmodium vivax (tertian)

Plasmodium ovale (tertian)

Plasmodium falciparum (tertian)

Plasmodium malariae (quartan)

Life cycle of malaria:

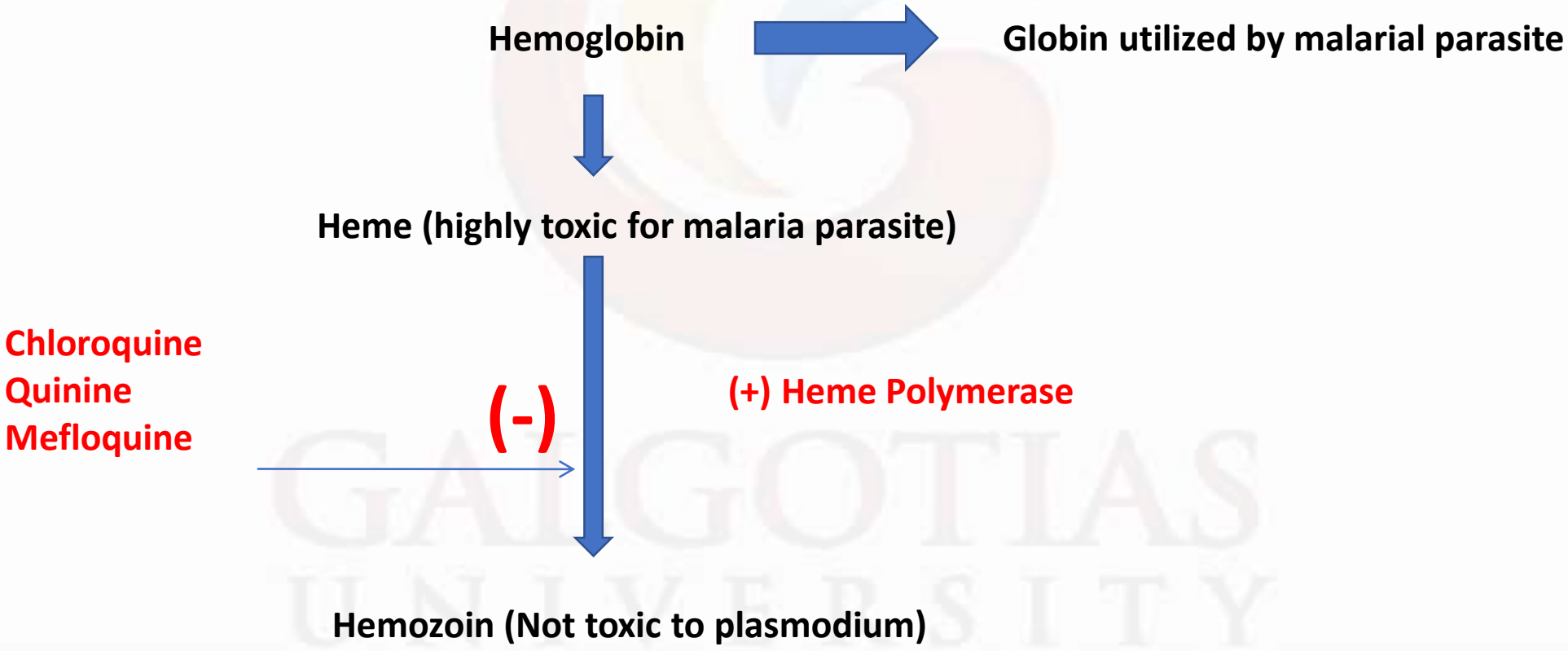


Classification :

4-Aminoquinolines-	Chloroquine (CQ)
	Amodiaquine (AQ)
	Piperaquine
Quinoline-methanol-	Mefloquine
Cinchona alkaloid-	Quinine, Quinidine
Diaminopyrimidine-	Pyrimethamine
8-Aminoquinoline-	Primaquine
	Tafenoquine
Sulfonamides-	Sulfadoxine
Antibiotics-	Tetracycline
	Doxycycline
	Clindamycin
Sesquiterpine-	Artemether
Naphthoquinone-	Atovaquone

Chloroquine:

- It is a rapidly acting erythrocytic schizontocide against all species of plasmodia



Pharmacokinetics

Oral absorption of CQ is excellent. About 50% gets bound in the plasma. It has high affinity for melanin and nuclear chromatin: gets tightly bound to these tissue constituents and is concentrated in liver, spleen, kidney, lungs (several hundred-fold), skin,leucocytes and some other tissues. Its selective accumulation in retina is responsible for the ocular toxicity seen with prolonged use. Chloroquine is partly metabolized by liver and slowly excreted in urine. The early plasma t½ varies from 3–10 days. Because of tight tissue binding, small amounts persist in the body with a terminal t½ of 1–2 months

- **Uses:** rapid fever, Extraintestinal amoebiasis, Rheumatoid arthritis

Pyrimethamine:

- It is a directly acting inhibitor of plasmoidal DHFRase.
- Pyrimethamine is more potent than proguanil, and a slowly acting erythrocytic schizontocid.
- Tasteless so suitable for children

- Adverse events: megaloblastic anemia, thrombocytopenia, agranulocytosis.

Proguanil :

- Biguanide converted to cycloguanil active compound
- Act slowly on erythrocytic stage of vivax & falciparum
- Prevents development of gametes

MOA: Dihydrofolate reductase inhibitors

Adverse effects: Stomatitis, mouth ulcers, larger doses depression of myocardium , megaloblastic anemia

ARTEMISININ DERIVATIVES:

Artemisinin is the active principle of the plant *Artemisia annua used in Chinese traditional* medicine as ‘Quinghaosu’.

It is a sesquiterpine lactone endoperoxide active against *P. falciparum resistant to all other antimalarial* drugs as well as sensitive strains and other malarial species. Potent and rapid blood schizontocide action is exerted

Mechanism of action:

The endoperoxide bridge in its molecule appears to interact with haeme in the parasite. Ferrous iron-mediated cleavage of the bridge releases a highly reactive free radical species that binds to membrane proteins, causes lipid peroxidation, damages endoplasmic reticulum, and ultimately results in lysis of the parasite.

Pharmacokinetics

Artemether: It is lipid-soluble and is administered orally or i.m., but not i.v. Absorption after oral as well as i.m. dosing is slower taking 2–6 hours. It undergoes substantial first pass metabolism and is converted to DHA. Extensive metabolism by CYP3A4 yields a variable t½ of 3–10 hours.

Uses: Uncomplicated falciparum malaria

Antifungal Drugs:

Fungi are universally present in nature but only a few are pathogenic to man. They belong to the Eumycetes group. Fungi need organic compounds as nutrients and they function as scavengers, breaking down complex carbohydrates and proteins of the dead bodies of other organisms. Fungal infection is termed as mycoses.

Types of Anti-fungal Drugs

- **Polyenes**

  Amphotericin B (AMB)

  It is obtained from *Streptomyces nodosus*. *Amphotericin B* is an amphoteric polyene macrolide (polyene = containing many double bonds; macrolide = containing a large lactone ring of 12 or more atoms) and gives fungicidal action. It is nearly insoluble in water (orally for topical infections), and is therefore prepared as a colloidal suspension of amphotericin B and sodium desoxycholate for intravenous injection (for systemic infections).

Mechanism of action

Amphotericin B binds with ergosterol (component of fungal cell membrane) → AMB–ergosterol complex alter the membrane permeability → creates pore in the membrane → pores allows the leakage of intracellular ions, amino acids, and micromolecules → cell death.

- **Clinical uses**

  AMB topically applied for oral, vaginal and cutaneous candidasis and paretrally used for systemic infections. AMB is the most effective drug for resistant case of kala–azar.

Adverse effects:

- Fever, chills, muscle rigor, hypotension (histamine release) occur during i.v. infusion

Heterocyclic benzofuran

- **Griseofulvin**

  It is isolated from *Penicillium griseofulvum and cures* infections due to dermatophytes (ringworm) when administered orally.

  It is ineffective against *Candida albicans*.

Mechanism of action:

Griseofulvin interacts with microtubules of mitotic spindleand with cytoplasmic microtubules → disorientation of mitotic microtubules and interferes in the mitosis → inhibits the growth of fungal hyphae.

- **Antimetabolite- (Flucytosine (5–FC)**

  It is pyrimidine analogue related to the chemotherapeutic agent 5–FU (5–fluorouracil).

Mechanism of action:

This permeates the fungal cell wall and converts into 5–fluorouracil → phosphorylation of 5–FU and formation of UDP and UTP → which inhibits to thymidylate synthesis → inhibits the DNA and RNA synthesis → inhibits the fungal cell growth.

Adverse effect Bone marrow depression, Leucopenia, rash, diarrhoea, *hepatitis.*

- **Azoles**

(A) Imidazoles (Topical): Clortimazole, Econazole, Miconazole, (Systemic): Ketoconazole

(B) Triazoles (Systemic): Fluconzole, Itraconzole

Mechanism of azoles:

Inhibits the fungal cytocrome enzyme lanosterol 14–demethylase → impair ergosterol synthesis.

Adverse effect:

- Nausea and vomiting (reduced by giving with meals).
- decreases androgen production and displaces testosterone from protein binding sites → Gynaecomastia, loss of libido, and hair, and oligozoospermia.
- Menstrual irregularities in the females

Antiviral Drugs:

Viruses are the ultimate expression of parasitism. They not only take nutrition from the host cell but also direct its metabolic machinery to synthesize new virus particles.

Classification:

1. ***Anti-Herpes virus****:* Idoxuridine, Trifluridine, Acyclovir, Valacyclovir, Famciclovir, Ganciclovir, Valganciclovir, Cidofovir, Foscarnet, Fomivirsen

2. ***Anti-Influenza virus:*** Amantadine, Rimantadine, Oseltamivir, Zanamivir

3. ***Anti-Hepatitis virus/Nonselective antiviral drugs:*** Lamivudine, Adefovir dipivoxil, Tenofovir

4. ***Anti-Retrovirus:***

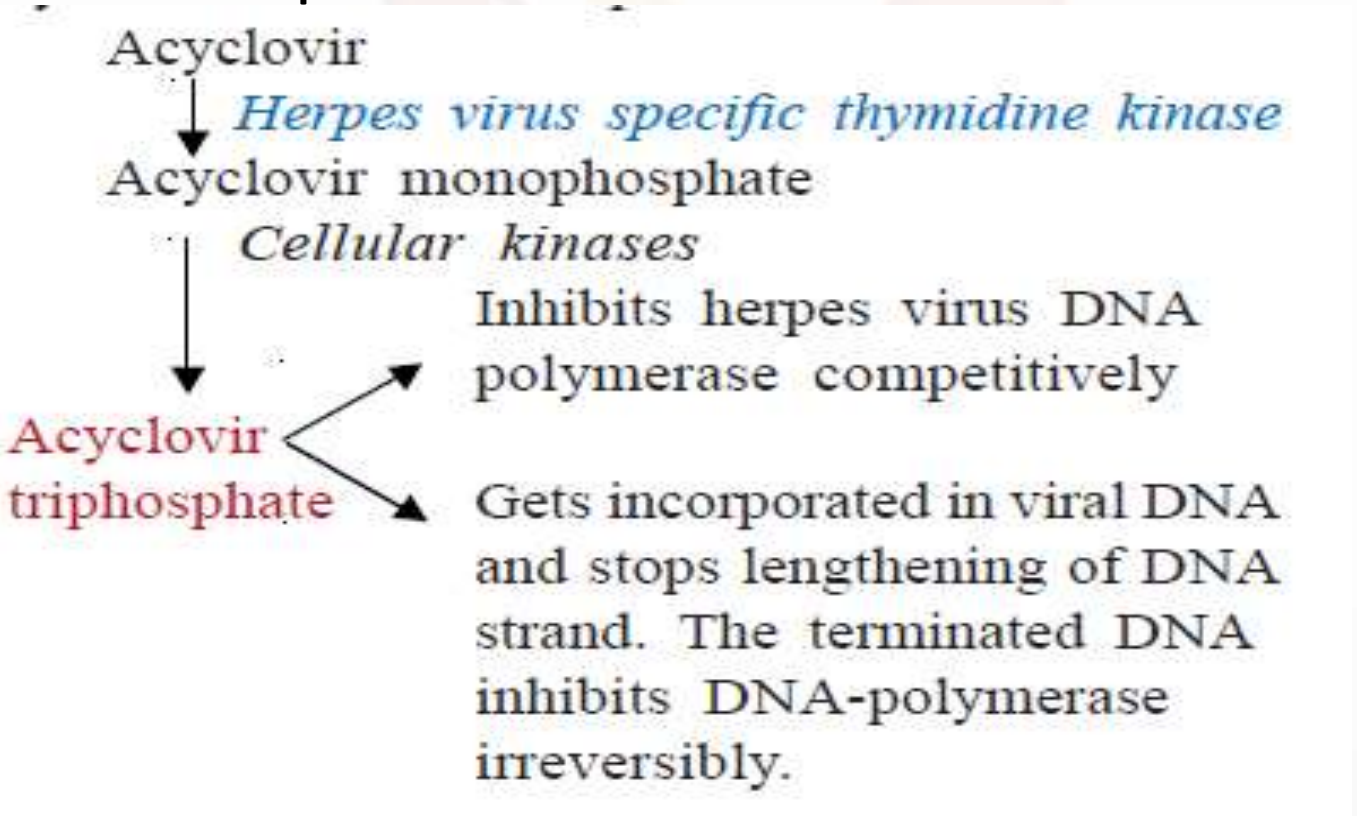
a) Nucleoside reverse transcriptase inhibitors (NRTIs): Zidovudine, Lamivudine, Abacavir, Emtricitabine

b) Nonnucleoside reverse transcriptase inhibitors (NNRTIs)*:*Nevirapine, Efavirenz, Delavirdine

c) ***Protease inhibitors****:*Ritonavir, Atazanavir, Indinavir, Nelfinavir

Acyclovir

- This deoxiguanosine analogue antiviral drug requires a virus specific enzyme for conversion to the active metabolite that inhibits DNA synthesis and viral replication.



Pharmacokinetics:

Only about 20% of an oral dose of acyclovir is absorbed. It is little plasma protein bound and is widely distributed attaining CSF concentration that is 50% of plasma concentration. After topical application, it penetrates cornea well. Acyclovir is primarily excreted unchanged in urine, both by glomerular filtration and tubular secretion; plasma t½ is 2–3 hours.

Uses:

1. *Genital Herpes simplex*
2. *Mucocutaneous H. simplex*
3. *H. simplex encephalitis*
4. *Herpes zoster*
5. *Chickenpox*

Adverse effects: Rashes, sweating, emesis and fall in BP occur only in few patients.

NRTIs

NRTIs in the presence of host cell thymidine kinase converts into active triphosphate metabolite (nucleotides) → competes with corresponding nucleotide for incorporation into viral DNA → inhibits reverse transcriptase enzyme and termination of viral DNA synthesis.

Zidovudine (AZT)

It is thymidine analogue and also known as azidothymidine. It is converted into active triphosphate metabolite and incorporates in the viral DNA that inhibit revesrse transcriptase enzyme and terminate the DNA chain synthesis.

Adverse effects:

- All NRTIs shows lactic acidosis, hepatic steatosis and lipodystrophy
- *Bonemarrow suppression–anaemia*, *neutropenia;* gastrointestinal intolerance, headache.

NNRTI s

NNRTIs Drugs bind directly to reverse transcriptase and disrupte catalytic site. Hence NNRTIs do not require phosphorylation for activity.

These drugs have cross resistance in different NNRTIs.

- Efavirenz is most potent NNRTIs for these reasons, it is preferred to give NNRTI for initial treatment of adult patients with HIV infection.

Adverse effects

- All NNRTI: rash (most common). Rash can progress to Stevens–Johnson syndrome.
- Nevirapine: Haepatotoxicity, rash including Stevens– Johnson syndrome, induces the metabolism of protease inhibitors and oral contraceptives.
- Efavirenz: *Neuropsychiatric reactions and teratogenic*

Protease inhibitors

- ***Protease inhibitors bind to the active site of protease enzyme*** → prevents the cleavage of gag–pol polyprotein → inhibit the maturation of virus → resulting production of immature, non-infectious viral particles.
- All PI metabolized in the liver and excreted in the fecal.

Adverse effects:

All protease inhibitors: *lipdystrophy (fat accumulation* Fat redistribution- Buffalo Hump), hyperlipidemia, insulin resistance and diabetes, elevated liver function tests, inhibits metabolism of other protease inhibitors.

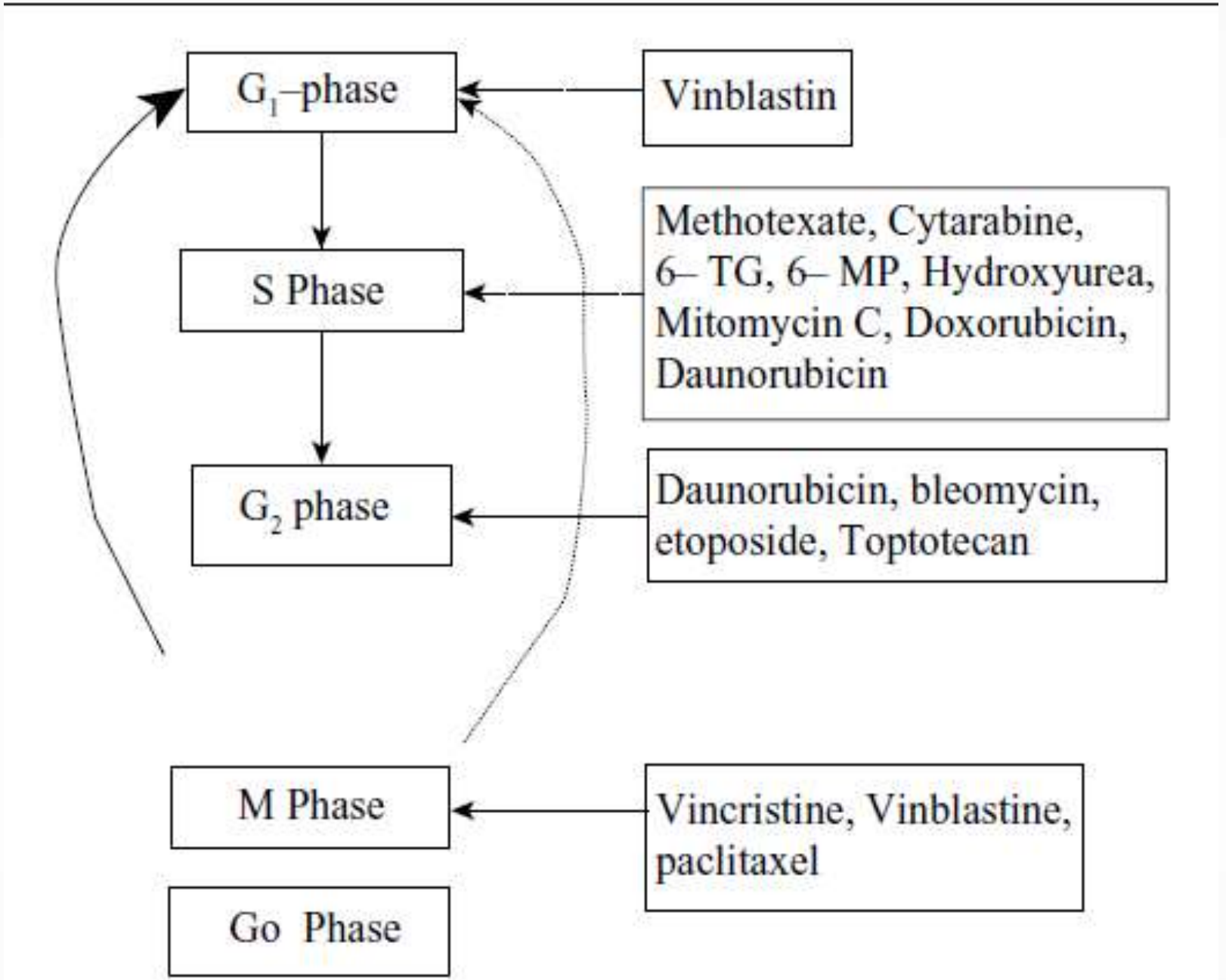
Anticancer drugs:

- Cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells. All cancers involve the malfunction of genes that control cell growth and division.

- Carcinomas: Malignant growths arising from epithelial cells.
- Sarcomas: Malignant growths of muscle or connective tissue.
- Adenocarcinoma: Malignant tumor arising from glandular tissue

Cell Cycle Specificity

- Cell cycle specific (CCS): Drugs that act on cells that are actively proliferating → schedule dependent. In most cases, CCS drugs are also phase specific.
- Cell cycle non-specific: Drugs acting on non– proliferating cells → dose-dependent.
- Cell cycle non-specific: Chlorambucil, cyclophosphamide, L–asparginase, cisplatin, procarbazine


G1–phase
Vinblastin
S Phase
Methotexate, Cytarabine,
6– TG, 6– MP, Hydroxyurea,
Mitomycin C, Doxorubicin,
Daunorubicin
G2 phase
Daunorubicin, bleomycin,
etoposide, Toptotecan
M Phase
Vincristine, Vinblastine,
paclitaxel
Go Phase

Drug	Mechanism of Action	Uses	Adverse effects
Methotrexate	Antimetabolite-inhibits DHF reductase (S phase)	Leukemias, lymphomas, breast Cancer; Rheumatoid arthritis, psoriasis	BMS, mucositis, crystalluria; leucovorin (folic acid) rescue decrease the incidence of adverse effect of Methotrexate
Cyclophosphamide	Alkylating agent–attacks guanine N7–dysfunctions of DNA	Non-Hodgkin's, ovarian, breast CA, neuroblastoma	BMS, mucositis, *hemorrhagic cystitis (Mesna-traps acrolein* and it is used to reduce acrolein toxicity), hepatotoxicity (high dose)
Nitrosourea; Carmustine (BCNU) Lomustine (CCNU) Dacrabazine	Highly lipid soluble alkylating agent and penetrate into CNS blood barrier. Dacrbazine primary affect the RNA synthesis while all other alkylting agent primarily affect to DNA	Meningeal leukemia and brain tumor	Nausea, vomiting
Cisplatin	Alkylating agent cross Nephrotoxicity (hydrate and use links DNA strands	Testicular, ovarian, bladder, lung Cancer	Nephrotoxicity (hydrate and use mannitol), neurotoxicity (deafness)
Etoposide and Teniposide	Increases degradation of DNA By interaction with topoisomeraseII	Lung (smallcell), prostate, and testicular carcinoma.	Gastrointestinal irritations, alopecia and bone marrow suppression.

Drug	Mechanism of Action	Uses	Adverse effects
Procarbazine	Alkylating agent	Hodgkin's (MOPP)	BMS, pulmonary toxicity, hemolysis, neurotoxicity, leukemogenic
Doxorubicin	Intercalator, forms free radicals, inhibits topoisomerase II	Hodgkin's (ABVD), breast, endometrial, lung, ovarian CA	BMS-delayed CHF (dexrazoxane, free radical trapper protects), alopecia, vesicant, radiation "recall"
6–Mercaptopurine	Purine antimetabolite (S phase) bioactivated by HGPR transferase	Acute lymphocytic leukemia immunosuppression (azathioprine forms 6–MP)	BMS, hepatotoxicity (jaundice, necrosis), GI distress
Vincristine and Vinblastine	↓ Microtubular polyrnerization-spindle poisons (M phase)	Vinblastine–Hodgkin's (ABVD), testicular CA, Kaposis's sarcoma vincristine–Hodgkin's (MOPP), leukemias, Wilms'	BMS, GI, alopecia Neurotoxicity (neuropathy)
Taxens: Paclitaxel	Promotes microtubule assembly and arrests cell cycle and G2 & M-phases	Metastatic ovarian and breast carcinoma	Myelosuppression and 'stocking and glove neuropathy'

Immunosuppressant and Immunomodulating Agents

Immunosuppressants are the drugs that inhibit or prevent activity of the immune system. They are used in immunosuppressive therapy to:

- Prevent the rejection of transplanted organs and tissues (e.g., bone marrow, heart, kidney, liver)
- Treat autoimmune diseases or diseases that are most likely of autoimmune origin (e.g., rheumatoid arthritis, multiple sclerosis, myasthenia gravis, systemic lupus erythematosus, Crohn's disease, pemphigus, and ulcerative colitis).
- Treat some other non-autoimmune inflammatory diseases (e.g., long term allergic asthma control).

Drugs:

- T–cell inhibitors (calcineurin inhibitor): Cyclosporin, Tacrolimus, Sirolimus
- Cytotoxic drugs: Methotrexate, Cyclophoshamide, Azothioprine, Mycophentolate mofetil,
- Glucocorticoids: Prednisolone and others
- Antibodies: Daclixumab, Basiliximab Muromonab, Trastuzumab, Etanercept

Cyclosporin: It is cyclic polypeptide with 11 amino acids, obtained from a fungus.

MAO: Binds to cyclophilin → inhibits calcineurin (cytoplasmic phosphatase) → ↓ activation of T-cell transcription factors → decreases IL–2, IL–3, and interferon, TNFα etc.

Toxicity: Nephrotoxicity, hypertension, hyperglycemia, liver dysfunction, rise in BP, anorexia, precipitation of diabetes and hirsutism.

Uses: Renal, Liver, Heart, Bone marrow and other transplantations.

Mycophenolate Mofetil

Mycophenolate mofetil is a semisynthetic derivative of mycophenolic acid, isolated from the mold *Penicillium glaucum.*

MAO: Mycophenolate mofetil is hydrolyzed into mycophenolic acid which inhibits inosinemonophosphate dehydrogenase → leads to inhibtion of De novo (guanosine nucletotides) purine synthesis

Adverse effect: Gastrointestinal disturbances (nausea and vomiting, diarrhoea, abdominal pain) and myelosuppression (primarily neutropenia).

Azathioprine

Azathioprine is a derivative of mercaptopurine and, like the parent drug, functions as a structural analog or antimetabolite. Azothioprine converts into mercaptopurine which inhibits De novo purine synthesis and damages DNA.

- **Used in the prevention of renal graft rejection.**
- **Adverse effect:** Bone marrow suppression and leucopenia. Leflunomide Leflunomide is a prodrug of an inhibitor of pyrimidine synthesis and used in rheumatoid arthritis. Toxicity Elevation of liver enzymes with some risk of liver damage, renal impairment, and teratogenic effects.

Immunomodulating Agents

- These agents modulate the immune response rather than suppress and major potential uses are in immunodeficiency disorders, chronic infectious diseases, and cancer; E.g., BCG vaccine and levamisole.

- BCG is a viable strain of *Mycobacterium bovis that has* used for immunization against tuberculosis.
- Levamisole increases the magnitude of delayed hypersensitivity or T cell-mediated immunity in humans. In immune deficiency associated with Hodgkin's disease, levamisole has been noted to increase the number of T cells in vitro and to enhance skin test reactivity.

Cytokines	Action
IFN–α	Treatment of several neoplasms, including hairy cell leukemia, chronic myelogenous leukemia, malignant melanoma, and Kaposi's sarcoma, and hepatitis B andC.
IFN–β	Relapsing-type multiple sclerosis
IFN–γ	Chronic granulomatous disease
IL–2	Metastatic renal cell carcinoma and malignant melanoma

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