PC
Pharmacology Concepts
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# Anti Cancer Drugs

Website

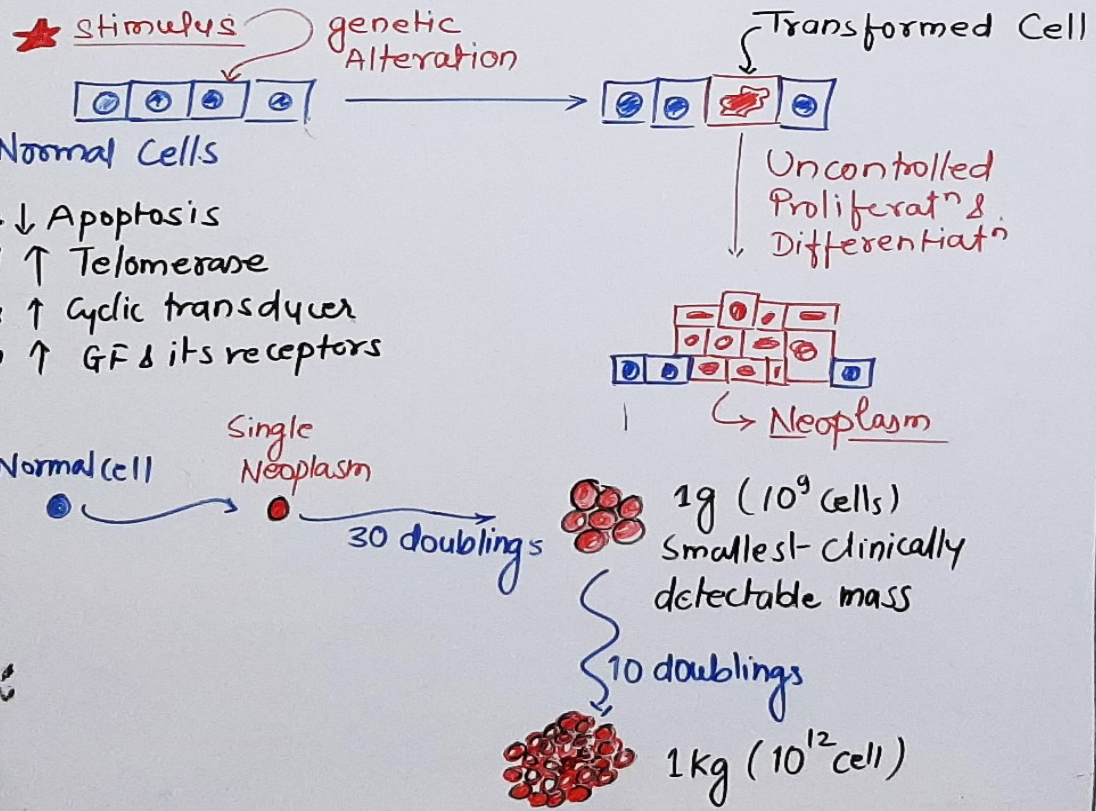
Videos

Pharmacology 3

# CANCER / NEOPLASM

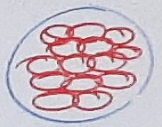
"Neoplasm" – Abnormal mass or tissue = "Tumor"
"Neoplasia" – Process of "new growth" of Neoplastic cells

FEATURES – 1. Uncontrolled Proliferation ( Rapid ↑ in no. of cell)
2. Uncontrolled differentiation & loss of it function
3. Invasiveness – Tendency to spread over healthy cell
4. Metastesis – spreding over different part of body
5. Acquired heredity & abnormal metabolic activity

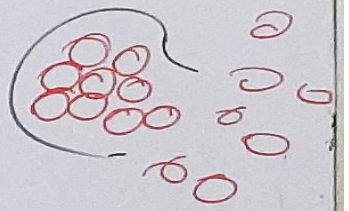



- ↓ Apoptosis
- ↑ Telomerase
- ↑ Cyclic transducer
- ↑ GF & its receptors

## Types of Tumors



(A) Benign Tumors ( Non-Cancerous)
↳ Fibroma – fibroblastic cell
↳ Osteoma – Osteoblast
↳ Chondroma – Cartilage
↳ Lipoma – Adipose tissue



(B) Malignant Tumors (Cancerous)

(1) Sarcoma – Mesenchymal tissue;-
little connective tissue (bone, cartilage, fats)
↳ Fibrosarcoma, liposarcoma, leiomyosarcoma

2. Carcinoma – Epithelial Cell origin
↳ Adenocarcinoma – Glandular → lungs, GIT, Breast, liver, ovaries, kidney, prostate cancer
↳ Squemous cell CA – oropharynx, larynx, esophagous, lungs, skin, cervix
↳ Transitional – Bladder, ureter, Renal Pelvis

3. Others: (A) Lymphomas – Lymphoid System
(B) Leukemias → WBC/ Leukocytes
(C) Malignant Melanoma – Melanocyte
(D) Gliomas – Astrocytoma, oligodendroglioma
(E) Seminomas – Testicular Origin
(F) Hepatomas – Hepatocyte

# CANCER – ETIOLOGY / PATHOGENESIS

Men – Lung, Prostate, Colorectal, Bladder, Lymphoma
Women – Breast, Lung, Colorectal, Endometrial, Lymphoma
Child – Leukaemia, brain, Bone Sarcoma, Endocrine, Soft-tissue

## Epidemiologic Factors / Etiology

### 1. Predisposing Factors :→

A) Genetic Factor :→ Retinoblastoma (missing of RB gene in chromosome 13), Breast (mutant BRCA-1 & 2) chromosome - 17 13

B) Racial & Geographical :→
Black Africans – Skin, Penis, Cervix & Liver
Indian – Oral, Breast, Liver, Colorectal etc

C) Environmental & Cultural :→
Smoking – Oral, GI, Lung, Pancreas, Bladder
Alcohol → Upper GI tract, Liver
Tobacco – Oral Cancer, Lung
Air Pollutant – Respiratory tract
Radiations – Skin

D) Age & Gender – ↑ risk >65 y

### 2. Chronic Non-Neoplastic (Pre-Malignant) Conditions –

A) Carcinoma in Situ :→
→ Malignancy are present in Epithelium without invasion across the basement membrane
→ Common sites for carcinoma in situ are uterine cervix, Oral Leukoplakia, intralobular & intraepithelial carcinoma of Breast

B) Benign Tumour → Adenocarcinoma, Neurofibrosarcoma

C) other Conditions :→
→ ulcerative Colitis → Colorectal cancer
→ Cirrhosis of Liver → Liver Cancer
– Chronic bronchitis → cancer of Bronchus
→ old burn Scar → Squamous cell Carcinoma
→ Infection – HIV, Hepatitis B & C, herpes, H. pylori, Aflatoxins

### 3. Hormones Related Cancer

→ Oestrogen — Endometrial Carcinoma
→ Oral Contraceptives — Breast Cancer
→ Anabolic Steroids → Benign & Malignant tumours

## PATHOGENESIS

Factors → Modification on Gene Exp.
→ (+) Proto-Oncogene → Oncogene
→ (–) of Tumour Supressor Gene
→ ↑Exp. of GF & R
→ ↑Cyclic transducers
→ Uncontrolled Proliferat^n & Differentiation
→ ↓Apoptosis & ↑ Telomerase Exp.
→ P° Tumour
→ Metalloproteinase
→ Metastasis
→ Secondary Tumour

# CARCINOGENS & GENESIS

Examples of Tumour Suppressor genes
↳ BRCA 1 & 2 → Breast Cancer — Cromosome 17 & 13
↳ RB → Retinoplastoma → C-13
↳ P53 → Osteosarcoma → C-17
↳ APC → Colon Cancer → C-5
↳ VHL → Renal Carcinoma — C-3

Examples of Targeted Oncogene & Cancer Cell line

↳ Her-2/ neu → Breast
↳ Cyclin D1 → Esophagus, Colon, Pencrease, Squamous
↳ K-ras$^{mut}$ → Pancreas
↳ Cyclin E → Liver
↳ B-Catenin → Colon
↳ Mut B-Raf → Melanoma

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CARCINOGEN :— are the agents, which may cause the cancer or carcinogenesis
e.g., - Chemicals, Raditions, Viral pathogens

1. Chemical Carcinogenesis / Mutagens

A.) Initiators :— they initiate the pathogenesis
↳ Direct acting comp. → bind covalently with cellular DNA
e.g., — Nitrogen Mustard, Benzyl chloride, Epoxides
↳ Indirect acting (pro-carcinogen) → Required metabolic Conversion
e.g → Nitrosamine → kidney, Liver, GI Cancer
→ Polycyclic aromatic Hydrocarbon — Lung
→ Aflatoxin B1 (Fungal inf) — Liver Cancer
→ Aromatic Amine / A20 dyes — Bladder
→ Metals - $Ni^{2+}$, $Pb^{2+}$, $Cd^{2+}$, $Co^{2+}$

B Promotors — promote cell. proliferatn & induce tumours in initiated cells. eg., Estrogen

# Test for Mutagenecity - AMES' Test
↳ check the mutation ability of chem. to induce mutatn in the mutant strain of Salmonella typhimyrium

2. PHYSICAL CARCINOGENESIS -
A.) Radition → UV Radition & Ionising Rad. - X-ray, B-ray, Y-rays
# UV → ↑ formatn of pyrimidine dimer → ↑ Mut. & Cell proliferatn, ↓ Cell death (Apoptosis)
# Ionising Raditions → emit protons & neutrones → Cancer
B) Non-Radiation — Asbestos inhation — Lung Cancer

3 INFECTION PATHOGENS → Affect Nucleic Acid — Mutation
Ⓐ Viruses → ↳ RNA retro (HIV-1) → T-cell leukamia / lymphoma
↳ Human Papilloma virus (DNA) → Squamous carcinoma - Cervix
↳ Hepatitis B & C → Hepatocellular Carcinoma
↳ Human Herpes Virus-8 → Kaposi Sarcoma
Ⓑ Bacteria → H. pylori → Gastric Lymphoma & G Carcinoma
Ⓒ Fungi → Aspergilus flavus → Aflatoxins — Liver Cancer

# BASIC PRINCIPLE OF CANCER THERAPY

**PRINCIPLE** – Chemotherapy of cancer is directed towards the arrest of Metabolic Site essential for cell replication.

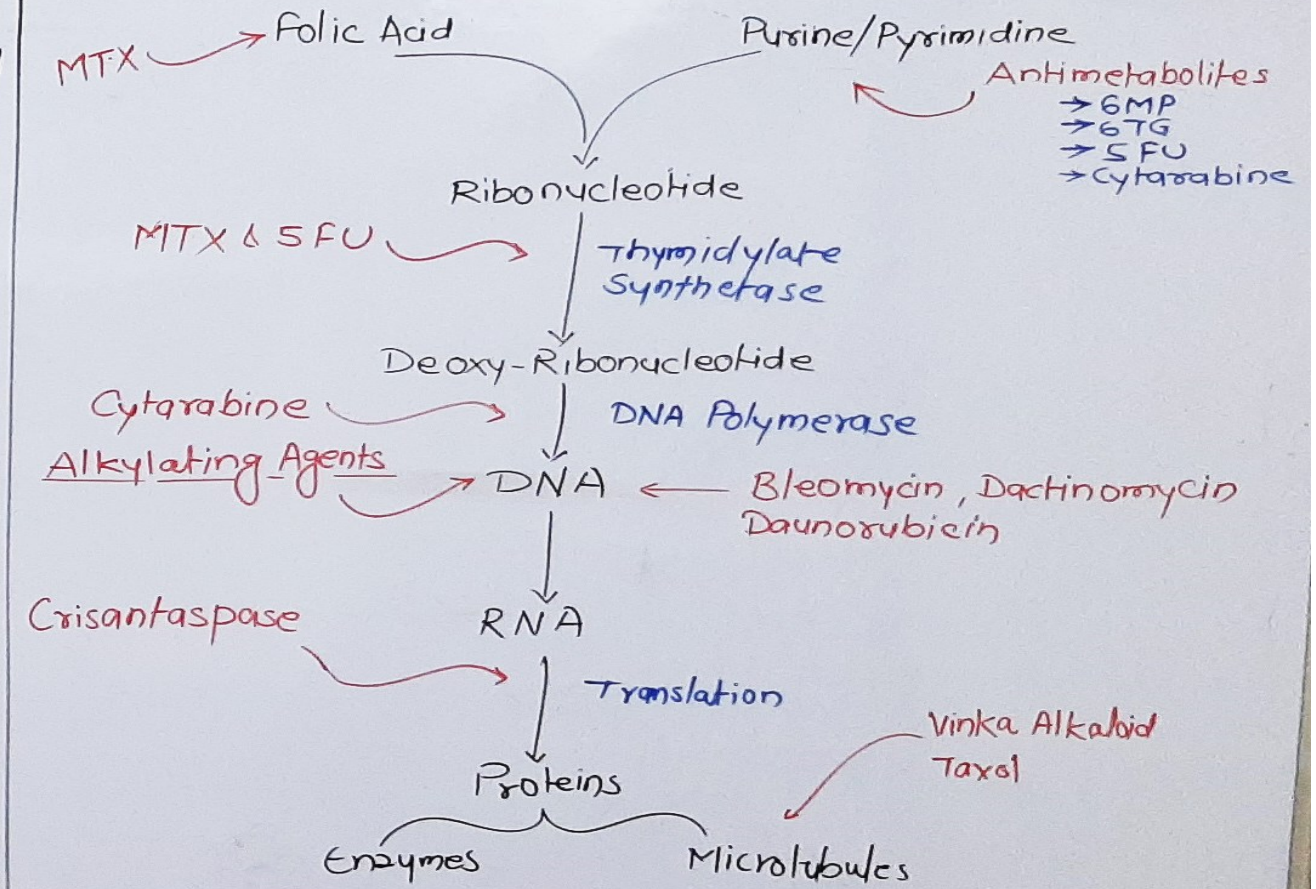
* Target Site → Nucleic Acid — DNA/RNA
* Target Molecules – Purine & Pyrimidine
* Main Action → ↓Cell Division

1. Non-Specific → Alkylating Agents, Actinomycin-D
2. Cell Cyclic Specific – Act on specific phase

↳ A) G 1 phase/Gap1 → Proceed of DNA Synthesis
e.g. - Vinka Alkaloids
↳ B) S- phase → DNA Synthesis – Antimetabolites
↳ C) G 2 phase → Terminal of DNA Syn. – Daunorubicin, Bleomycin, Etoposide
↳ D) M phase → Mitotic phase – Vinka, Taxol

## GENERAL PROBLEM/DIFFICULTIES →

↳ 1. Not Specific Metabolic pathways – Cancer & host cell
↳ 2. Narrow Safety of margine
↳ 3. Immunosupression
↳ 4. Resistance
↳ 5. General ADRs → ↳ Bone Marrow Supression
↳ Alopecia, Impotency
↳ GIT disturbance
↳ Teratogenic
↳ Carcinogenecity
↳ Hyperuricemia




## RESISTANCE : → Transport Defect. P-glycoproteins

↳ ↓ uptake System (MTX)
↳ Insufficient Metabolic activatn of drug (6 MP, 5 FU)
↳ ↓ Affinity to targeted Enzyme
↳ Rapid repair of drug-induced lesion

# ANTI NEOPLASTIC AGENTS

1 Alkylating Agents :-

ⓐ Nitrogen Mustard – Cyclophosphamide, Chlorambucil
ⓑ Nitrosoureas – Carmustine, Lomustine
ⓒ Alkyl Sulphonate – Busulfan
ⓓ Ethylenimines – Thiotepa
ⓔ Triazenes – Dicarbazine

↳ Carbonium Ion ⟵ $-NH_2$, $-SH$, $-OH$

2. Antimetabolites :- Metabolic Inhibitors

ⓐ Folate Antagonist – Methotrexate (MTX)
ⓑ Purine Analouges – 6-Mercaptopurine, 6-Thio-guanine, Azathioprime, Flutarabine, Pentostatin, Cladribine.
ⓒ Pyrimidine Analouge – 5-Fluorouracil, Cytarabine, Raltitrexed, Pemitrexed

3. Natural Product :- Ⓐ Plant products

# Vinka Alk (Vincristine, Vinblastine) → depolamerizat$^n$ of Microtubule
# Taxol (Paclitaxel, Docetaxel) – ↑ polymerizat$^n$ of microtubules
# Campothecins (Irinotecan, Topotecan) → × Topoisomerase I
# Podophyllotoxin & Etoposoide → × Topoisomerase II
Ⓑ Antibiotics – Actinomycin-D, Doxorubicin, Daunorubicin, Bleomycin, Mitomycin-C

↳ Affect DNA

Ⓒ Hormones & Antihormones

# Glucocorticoide – Prednisone
# Estrogen – Fosfestrol, Diethylstilbesterol
# Anti Estrogen – Tamoxifen
# Anti-Androgen – Flutamide, Bicalutamide
# Progestins – Medroxy progesterone, Hydroxy progesterone
# GnRH Analouge – Naferelin, Goserelin
# 5-α-reductase Inhibitors – Finasteride, Dutasteride

Ⓓ Enzyme – L-Asparginase

Ⓔ Biological Response Modifiers – Interferons (α, β, & γ)

5. Other Agents – Cisplatin, Hydroxyurea, Procarbazine

6. Future Aspect :-

# Angiogenesis & Metalloproteinase inhibitors
# COX-2 Inhibitors
# Activat$^n$ of tumour supressor gene – $p^{53}$
# Antisense oligonucleotides
# Gene therapy

# PHARMACOLOGY OF CYCLOPHOSPHAMIDE

**Alkylating Agents** - They cause alkylation of suitable receptor site by transfering an alkyl radical

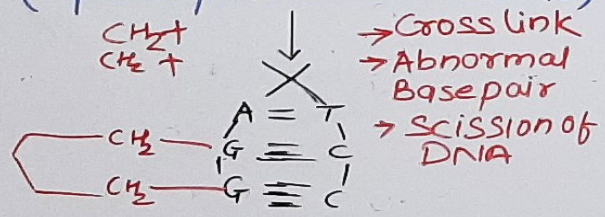
# These drugs are Bifunctional; they have 2 alkylating group / $-\overset{+}{C}H_2$ / $-\overset{+}{C}H_2$ or highly reacting Carbonium ion (C+)

# This Carbonium ion covalently bind with nucleophilic mole ($-NH_2$, $-SH$, $-OH$, $-PO_4$) present in the DNA & can cause crosslinking between them.

# Bifunctional alkylating agent can cause intrastand cross linking of two nucleophilic site such as $N_7$ of Guanine, $N_1$ & $N_3$ of Adenine, & $N_3$ of Cytosine

Cyclophosphamide ⟶ Aldophosphamide

Phosphoramide Mustard
(Cytotoxic / Anti cancer Molecule)



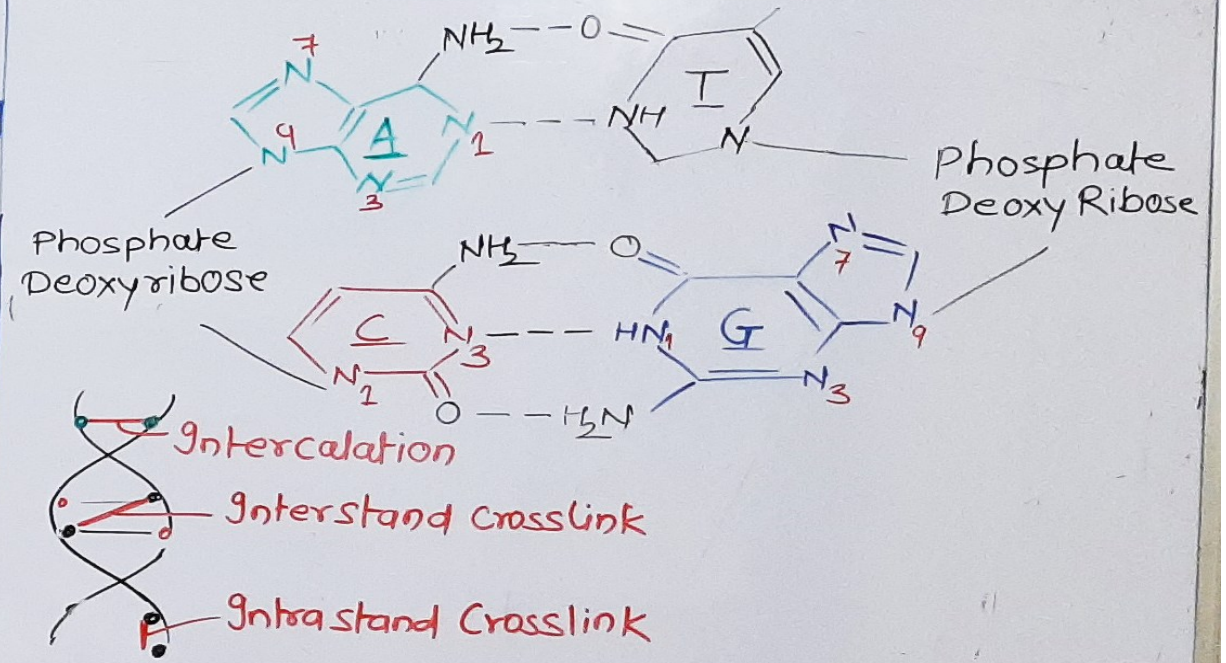

Acrolein
(toxic Metabolite)

ADR ↓
→ Bladder Damage
→ Alopecia
→ Cystitis

Mercaptoethane sulfonate (Mesna)
(Antidote)

**Uses** - Hodgkin's Dis (Lymphoma)
↳ Lung Carcinoma
↳ Solid tumours
↳ Lymphatic leukemia
↳ Wilm's tumour
↳ Ovarian cancer

Oral - 2-3 mg/kg/day
IV - 10-15 mg/kg - 7-10 day
IM




# Nitrogen Mustard - Radiomimic Anticancer drugs

# Nitrosourea (Carmustin & Lomustin) → highly lipid soluble thus used in Brain tumour & Meninges carcinoma

# Alkylsufonate (Busulfan) - selective effect on Bone Marrow & ↓ formatn of platelets & Granulocytes, thus used in Granulocytic leukemia

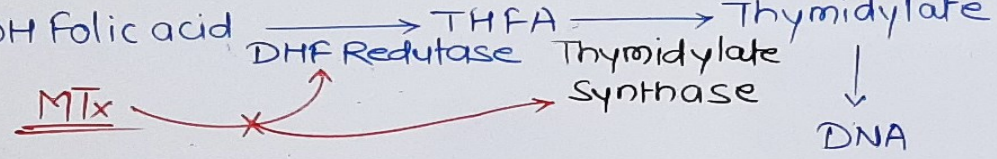
# Triazene (Dacarbazine) - Malignant Melanoma

# Ethylenimine (Thiotepa) - Breast & Ovarian Cancer

# PHARACOLOGY OF ANTIMETABOLITE – MTX

# They inhibit the utelizatn of normal substrate for DNA Synthesis by inhibiting enzyme or act as a substrate analouge. ↓ S-phase

Folate Antagonist – Methotrexate, Pemetrexate




# 50000 times higher affinity for DHFR than normal DHFA
# It has low lipid solubility, does not cross BBB.
# Actively taken up by folate transport system & metabolized in to highly active polyglutamate derivetive through Folypolyglutamate Synthase,
# Little metabolized & Largly excreted through urine

Uses:– # Acute Lymphoblastic leukamia
# Choriocarcinoma (15-30 mg/day orally, for 5 days)
# Non-Hodgkin lymphoma (Lymphatic system)
# Breast, Bladder, testes, neck cancer
# Burkitt's lymphoma – cancer starts in B-cell

ADR: # Major effects/toxic on Bone Merrow –
low dose – megaloblastic Anaemia
high dose – Pancytopenia

# Mucositis & Diarrhoea
# GI destyrbance & bleeding

Antidotes :–
# Toxicity of MTx can not overcome by Folic acid, because it will not be converted into active Co-Enz form (THFA)
# Folinic Acid ($N^5$ Formyl THFA & Citrovorum factor)
# Thymidine also counteract MTx toxicity

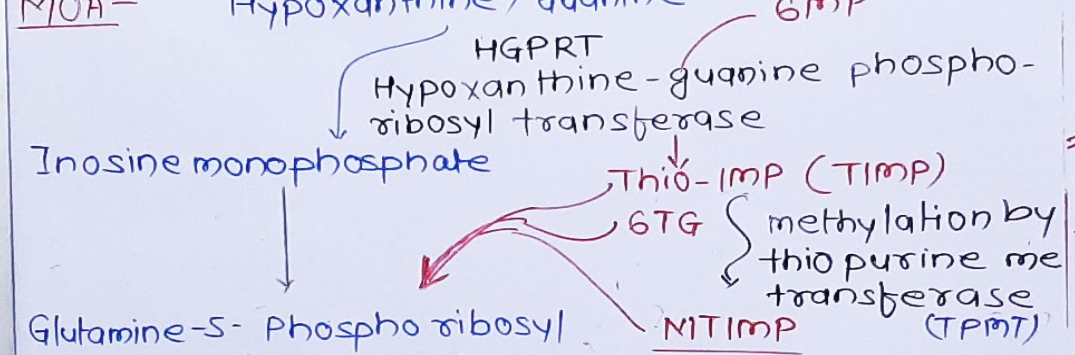
Drug Interaction :–
# Salicylate, Sulfonamide → displace its Protein Binding Site ↓ ↑ free/Plasma Conc. – ↑ Toxicity
# Aspirin, Sulfonamide → ↓ Renal Tubuler Secretion ↑

Pemetrexate :– Newer derivetive of MTx
MOA → P° Thymidylate Synthase inhibitor, Also DHF Reductase inhibitor
# ADR- Myelosupression (BMS), mucositis, diarrhoea similar as MTx,
# But painful, itching erythromatous rash, mostly involving the hand & feet (Hand-Foot Syndrome) – that is relieve by Dexamethasone pretreatment
# Folic acid & Vit B12 pretreatment for – ↓ Myelosupression
Use = Pem + Cisplatin → Mesoepithelioma, Lung carcinoma
# Breast, Bladder & Colorectal Cancer

## MERCAPTOPURINE (6MP) & THIOGUANINE (6-TG)

# Antimetabolite – Purine Analogue

MOA –




Uses :- Childhood Acute Leukaemia, Solid tumours, Choriocarcinoma

P'kinetics – Absorbed orally, *6-MP metabolised in liver by Xanthine oxidase Ezn., *6TG metabolised by S-methylatn

ADR :- # Bone Marrow Suppression (TPMT deficient patient has higher in risk)
# Reversible Jaundice - (6MP)
# Hyperuricaemia (6MP, 6TG), reduced by Allopurinol

AZATHIOPRINE :- # Marked effect on T-lymphocyte & supress the cell mediated immune system
# Used as immunosupressant in Organ transplant & R. Arthritis
# Metabolised by Xanthine oxd.
# Azathioprine → 6mp

## FLUOROURACIL (5-FU)

# Pyrimidine Analogue → Anticancer, Antifungal, Antipsoriatic

MOA – 5FU → 5fluoro 2'-deoxyuridine 5'phosphate (FdUMP)

2-deoxyuridylic a —Thymidylate Synthaase→ 2deoxythymidylic acid → DNA & RNA

# "Thymineless Death"
# Thymidine - can partially reversed the 5FU toxicity
# Inhibition of TS by 5FU depends upon the presence on THFA. Leucovorin infusion along with 5FU, enhance the efficacy of 5FU
# Cisplatin / Oxaliplatin - Synergise the effect
# "FOLFOX" – Leucovorin + 5FU + Oxaliplatin

P'kinetics – Unreliable orall abs. thus used by I.V.
# Metabolised by Dihydropyridine Dehydrogenase, Rapidly
# Plasma $t_{1/2}$ = 15-20 min. after IV infusion
# Genetic deficiency of DPD → Sever 5FU toxicity

ADR = Myelosuppresion (BMS), Mucositis, Peripheral neuropathy (hand-foot syndrome)

Uses :- Stomach, Colon, rectum, Pancreas, Liver, Bladder Cancer

- Raltitrexed & Pemetrexed → Thymidylate Synthase Inhibitor

# CYTARABINE (Ara-C, Cytosine Arabinoside) → Ara-c-triphosphate
# Inhibits DNA Polymerase
# used in Lymphoblastic leukaemia, non-Hodgkin's lymphoma
# also used in Herpes infectn & Encephalitis
# ADR - BMS, Mucositis

## NATURARL DRUGS

### (A) Plants

1. Vinka – Vincristine, Vinblastine, Vindesine, Vinorelbin
   ↳ # "Spindle Poisons" – depolymerisatn of microtubules.
2. Taxols - Paclitaxel & Docetaxel -(Pacific Yew Tree)
   ↳ # Enhance the polymerisatn of microtubules
3. Podophyllotoxin & Etoposide -(P. peltatum)
   ↳ Inhibit Topoisomerase I Enzyme
4. Campothecins - Irinotecan & Topotecan (GII)
   ↳ Inhibit Topoisomerase II Enzyme

### B) Antibiotics :-

1. Actinomycin-D – "S. chrysomallus"
   ↳ Intercalates in minor groove of DNA & also inhibit DNA-dependent RNA Polymerase
2. Doxorubicin & Daunorubicin – "Anthracyclines"
   ↳ Intercalate DNA, & Inhibit Topoisomerase II
3. Bleomycin – Break the DNA Strands
4. Mithramycin – ↓ DNA-dependent RNA Polymerase

### C) Hormones Related Drugs -

1. Tamoxifen – Estrogen Receptor blocker, also induces TGF-β that inhibits growth malignant cell
2. 5-α Reductase Inhibitors - Finasteride, Dutasteride
   → Treatment of Enlarge prostate
   → Excessive hair growth in Women

### D. Enzyme – L-speraginase

Aspartic ā + Glutamic ā —Asp. Synthase→ Asperagine

Asperaginase ↓ metabolism

# Asperagine essential for Cell proliferation.

### E. Interferons →

- Induce product$^{n}$ of Translation Inhibitory Protein (TIP)
- Also direct Antiproliferative

## NEWER TARGETED DRUGS -

# BCR-ABL-Tyrosine kinase Inhibitors - Imatinib, Dastanib, Nilotinib

# EGF (HRE) Receptor Inhibitor - Gefitinib, Erlotinib, Cetuximab, Lapatinib

# Angiogenesis Inhibitors – Bevacizumab, Sunitinib,

# Proteasome Inhibitor – Bortezomib

# CD-20 Inhibitor - Rituximab