Purine Analog

★ 6-Mercaptopurine
Thioguanine

★ Cladribine
★ Fludarabine

Clofarabine
Nelarabin
Pentostatin.

6-MERCATOPURINE –

Hypoxanthine analog → (XO) → uric acid

Hypoxanthine guanine phosphosiboxyl transferase

6-Thioinosine monophosphate ⊣ Allopurinol

↓⊖

Ribosyl-5-P

↓⊖

Synthesis of Purine

6 Mercaptopurine —used in→ chronic de... choriocarcinoma.

- Leukemia – ALL

S/E – BM Supression, N,V,D Myelosupression
Hepatotoxicity.

if ↑ 6-Mercapopurine toxicity

Rx → ↓ dose of 6 MP to 1/4 of the original dose.

THIOGUANINE

- NOT a Hypoxanthine analogs
- Not metabolized by XO Enzyme

FLUDARABINE

- Flourinated Purine Analogs of Antiviral drug VIDARABINE.

↓
DOC for
CLL (FCR regimen)
Fludarabine, Cyclophosphamide, Rituximab

S/E → Interstitial Pneumonitis

CLADRIBINE

DOC – Hairy cell Leukemia
Refractory Histiocytosis

Azothioprine

thiouric acid ← XO ← 6MP → Methyl mercaptopurine (Inactive)

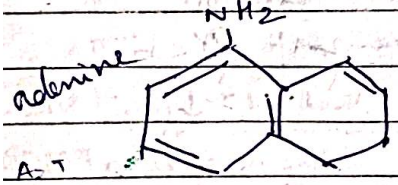
↓ HGPRT

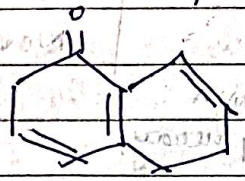
6-Thioinosine Monophosp (TIMP) ⊣ XO

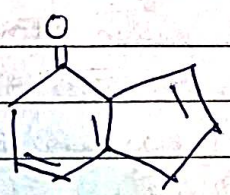
6 thio guanine nucleotide → DNA → apoptosis

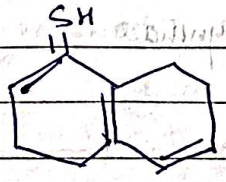
Methyl mercaptopurine Ribonucleotide → Purine Synth

[Thiopurine methyl transferase] (TPMT)









(Prodrug)

Azothioprine

if allopurinol given ⊖ XO.

HGPRT – 80%

↑ toxicity immunosuppression

100%

30% XO → thiouric acid ← 6MP → TPMT (20%) → Methyl mercaptopurine (inactive)

↓ HGPRT 50%

6TIMP ⊖ G = Purine ⊖ A

↓ 6-thioguanine nucleotide

↓ DNA

↓ apoptosis

6MP ⊖↓ Crohn's → ~~No immune Suppression~~ Syst.

TCell, BCell Blocked.

↓ No immune System.

↓ Methyl mercaptopurine Ribonucleotide

↓ x block PURINE Synthesis

Interaction

Warfarin

Allopurinol

Sulfamethaxazole

[6MP inversely ∝ to Allopurinol]

6MP ∝ 1/allopurinol → myelosuppression

6MP – Potent Immunosuppressant.

Etoposide → Human Topoisomerase

Adriamycin

Doxorubicin

6MBicaptopurin — Human DNA Polymerase

5FU — Thymidylate Synthase

Antibacterial agent:

Ciprofloxacin — Bacterial DNA gyrase

Nalidixic acid — "

Novobiocin — "

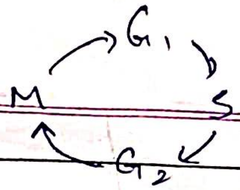
(antagonist)

AZACITIDINE

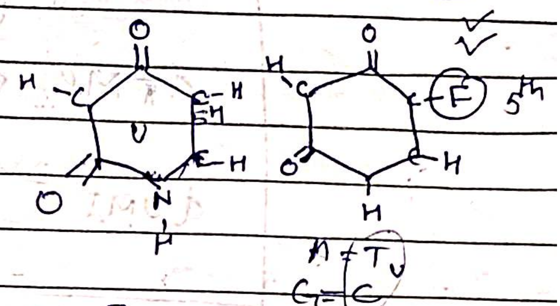
CYTARABINE

CAPICITABINE

GEMCITABINE



5FU



** 5- Fluro uracil

5FU → cell

5 FU

5FUTP & 5FUMP

↓ RNA (Flurine indeces RNA) RNA abnormal

↓ 5 F deoxy uridine MP (5-FdUMP) → compete → block

(compete ē actuvatib) ↓ 5FdUMP bind to Enzyme block conversion

dUMP ↓ → dTMP DNA Synthesis

MTX → ⊖ thymidylate Synthase

(coenzy) * N-5 N10MTHF

dUMP ✗→ dTMP

– deficiency of THYAMINE ↓

No Synthes of DNA

uses – Colorectal Ca, Br Ca, ovary, BHT BCC

A/E – * ALOPECIA

* Coronary vessel spasm Vasospasm

* MUCOSITIS

* Hand foot ds

" Palmar Plantar Erythro dysthesia

LEUCOVORIN (folinic acid) ē 5FU

N5 Formyl THF ↓ N5 N10 MTHF Cofactor

drug interactn Metotrexate (folate antagonist)

Antimetabolite Competitively ⊖ Ⓝ substance or get themself incorporated forming dysfx macromolecul

① FOLATE Antagonist

methotrexate & Pemetrexed.

MTx = ① FA analogue = highly effective

② act by = ↓ DHFRase (reductase) = block the conversion of DHFA → THFA

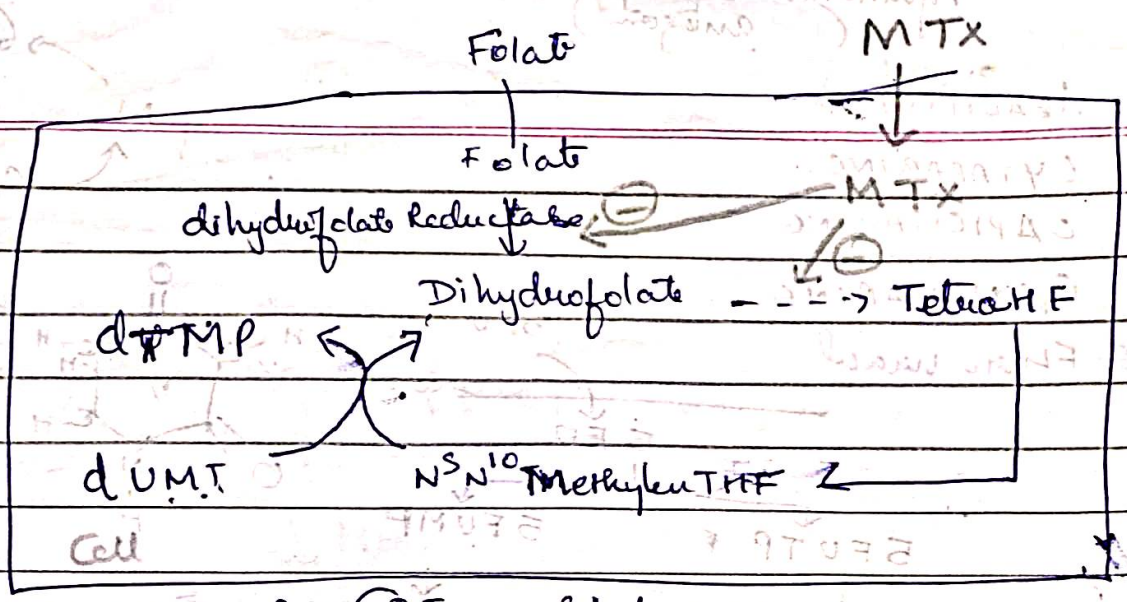
③ MTx utilize folate carrier to enter into cell and it transform into more

③ active – POLYGLUTAMATE form by Enz FOLY POLY Glutamate Synthase

THFA is a essential enzy required for – Purine Synthesis & AA interconversion (denovo) – Carbon transfer process

inhibition is Pseudoirreversible becoz MTx has – 50,000 times higher affinity for the enzyme than Ⓝ Substrate

MTX has cell cycle specific action = KILL cell in "S" Phase



MTX → ⊖ DHFR & ⊖ Thymidylate synthase.

↓ thymidylate = 1° affect DNA Synthesis

along ē RNA & protein affect

- Exert major toxicity on Bone marrow.
- Low dose given repeatedly → cause Megaloblastic Anemia.

S/E - Mucositis & diarrhea

Desquamation & bleeding occur - GIT

Indication → choriocarcinoma, ALL, Br Ca, bone Sarcoma

Psoriasis 2.5 mg/day, RA arthritis.

→ 1 mg/kg/day (MTX) 0.1 mg/kg/day (Leu