🧬 Antimetabolites (Cell Cycle-Specific Drugs)

🔑 Key Concept

- Most antimetabolites are S-phase specific (act during DNA synthesis) 🧪
- ❗ Exception: *Cladribine* → cell cycle NON-specific

💡 Core Mechanism (Big Picture)

Antimetabolites mimic normal nucleotides → get incorporated into DNA or block synthesis → halt DNA replication → cell death

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🔄 Flowchart: How Antimetabolites Work

Normal DNA synthesis → Requires purines + pyrimidines + enzymes → Antimetabolites interfere by → Inhibiting nucleotide synthesis OR incorporating faulty analogs into DNA → DNA replication failure → Cell death (especially rapidly dividing cells 💥)

📊 High-Yield Drug Table

Drug/Class	Mechanism	Clinical Use	Adverse Effects
Thiopurines (Azathioprine, 6-MP)	Purine analogs → ↓ de novo purine synthesis	RA, IBD, SLE, ALL, transplant rejection	Myelosuppression, hepatotoxicity
Cladribine, Pentostatin	Purine analogs resistant to ADA → DNA synthesis inhibition	Hairy cell leukemia	Myelosuppression

Cytarabine (Ara-C)	Pyrimidine analog → DNA chain termination	AML, lymphomas	Myelosuppression
5-Fluorouracil (5-FU)	Inhibits thymidylate synthase → ↓ dTMP	Colon, pancreatic cancer, BCC (topical)	Myelosuppression, hand-foot syndrome
Hydroxyurea	Inhibits ribonucleotide reductase	CML, polycythemia vera, sickle cell disease	Severe myelosuppression
Methotrexate	Inhibits DHFR → ↓ folate → ↓ DNA synthesis	Cancers + RA, psoriasis, ectopic pregnancy	Myelosuppression, hepatotoxicity

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🧪 Drug-by-Drug Notes

1️⃣ Thiopurines (Azathioprine, 6-Mercaptopurine)

💡 Mechanism

- Purine (thiol) analogs → inhibit de novo purine synthesis
- Azathioprine → converted to 6-MP
- Activation requires HGPRT enzyme

🔄 Flowchart: Thiopurine Activation

Azathioprine → Converted to 6-MP → Activated by HGPRT → Inhibits purine synthesis → ↓ DNA replication → Cell death

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⚠️ Important Drug Interaction

- 6-MP is broken down by xanthine oxidase → If patient takes allopurinol or febuxostat → ↓ metabolism of 6-MP → 🚨 Toxicity increases

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📌 Clinical Uses

- Autoimmune: RA, SLE, IBD
- Oncology: ALL
- Transplant: prevention of rejection

❗ Adverse Effects

- Myelosuppression 💉
- Hepatotoxicity
- GI upset

2️⃣ Cladribine & Pentostatin

💡 Mechanism

- Purine analogs resistant to ADA (adenosine deaminase) → Accumulate → disrupt DNA synthesis

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📌 Clinical Use

- Hairy cell leukemia (very high-yield 🎯)

❗ Adverse Effect

- Myelosuppression

3️⃣ Cytarabine (Ara-C)

💡 Mechanism

- Pyrimidine analog → Incorporates into DNA → Causes DNA chain termination → Also inhibits DNA polymerase

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📌 Clinical Use

- AML (VERY high-yield 💯)
- Lymphomas

❗ Adverse Effect

- Myelosuppression

4️⃣ 5-Fluorouracil (5-FU)

💡 Mechanism

- Converted to 5-FdUMP → Inhibits thymidylate synthase → ↓ dTMP → ↓ DNA synthesis → Tumor cell death

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⚠️ High-Yield Pearl

- Leucovorin enhances 5-FU effect → Stabilizes drug-enzyme complex → ↑ efficacy

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📌 Clinical Uses

- Colon cancer (classic association 💡)
- Pancreatic cancer
- Topical: actinic keratosis, basal cell carcinoma

❗ Adverse Effects

- Myelosuppression
- Hand-foot syndrome 🖐🦶 (palmar-plantar erythrodysesthesia)

🇸 Hydroxyurea

💡 Mechanism

- Inhibits ribonucleotide reductase → ↓ conversion of ribonucleotides → deoxyribonucleotides → ↓ DNA synthesis → ↓ cell proliferation → ↓ DNA synthesis

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📌 Clinical Uses

- Myeloproliferative disorders (CML, polycythemia vera)
- Sickle cell disease → ↑ HbF → reduces sickling 🩸

❗ Adverse Effects

- Severe myelosuppression
- Megaloblastic anemia

6️⃣ Methotrexate (MTX)

💡 Mechanism

- Folic acid analog → Inhibits dihydrofolate reductase (DHFR) conversion to ↓ tetrahydrofolate (THF) → ↓ dTMP → ↓ DNA synthesis → Cell death

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⚠️ High-Yield Pearl

- Leucovorin rescue🛟→ Bypasses DHFR → protects normal cells

📌 Clinical Uses

Cancers:

- ALL, lymphomas, choriocarcinoma, sarcomas

Non-cancer:

- RA, psoriasis, IBD
- Ectopic pregnancy
- Medical abortion (with misoprostol)

❗ Adverse Effects

- Myelosuppression (reversible with leucovorin)
- Hepatotoxicity

- Mucositis (mouth ulcers)
- Pulmonary fibrosis
- Teratogenic 🚫🤰
- Nephrotoxicity

🎯 Summary

- Most antimetabolites → S-phase specific
- Cladribine = exception (non-specific)
- Methotrexate & 5-FU both ↓ dTMP
- Leucovorin:
    - Enhances 5-FU
    - Rescues methotrexate toxicity
- Allopurinol + 6-MP = toxicity ⚠️
- Hydroxyurea → ↑ HbF in sickle cell

-> The End <-