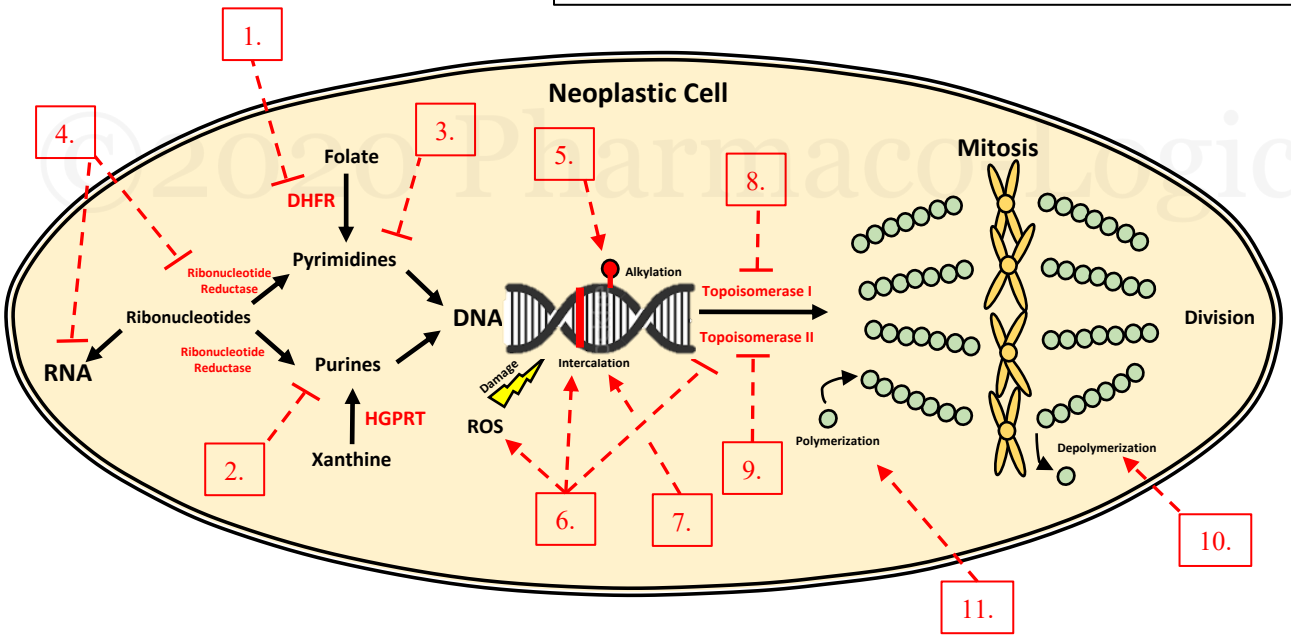
1. Folate Antagonists
MOA: Inhibitor of dihydrofolate reductase → decreased DNA synthesis in neoplastic cells (activated by FPGS) (S phase)
Methotrexate – Polyglutamated is more potent
Pemetrexed
Lometrexol
PK: Does not cross the BBB – given intrathecally, Renal elimination
USE: Breast (**CMF**), Choriocarcinoma, ALL, RA, Abortion (ectopic/molar)
Resistance: ↓ drug activation (FPGS), ↑ DHFR expression, ↓ drug transport
SE: Myelosup. Alopecia, GI, hepatotoxicity, nephrotoxicity, stomatitis, Preg Cat X. **Leucovorin rescue** – donates one carbon group - ↓ side effects

2. Purine Antagonists
MOA: Mimics DNA precursors → Leads to chain termination (S phase)
6-Mercaptopurine (6-MP) – activated by HGPRT, inactivated by TPMT/XO
Cladriabine – Hairy cell leukemia
6-thioguanine (6-TG) – activated by HGPRT, inactivated by TPMT
PK: Absorption decreased by food, does not cross the BBB
USE: *6-MP* – ALL, IBD, immunosuppression *6-TG* –AML, CML
Resistance: ↓ drug activation (HGPRT), ↑ inactivation (TPMT),
SE: Myelosuppression, hepatotoxicity, pancreatitis
DDI: Allopurinol – ↓excretion

3. Pyrimidine Antagonists
MOA: Mimics Uracil → 1. Inhibits Thymidylate synthase 2. Causes chain termination 3. inhibits RNA synthesis – Combined with leucovorin (↑ efficacy) (S phase)
5-fluorouracil (5-FU),
PK: inactivated by Dihydropyrimidine dehydrogenase (DPD), Crosses the BBB, parenteral
USE: Colorectal cancer (FOLFOX, FOLFIRI), Breast Cancer (CMF), BCC
Resistance: ↑ drug target (TS), ↑ DPD expression – causes 5-FU breakdown
SE: Myelosuppression, Neurotoxicity, Stomatitis, inflammation/irritation, photosensitivity

4. Gemcitabine, Cytarabine
MOA: Mimics Cytosine → 1. inhibits Ribonucleotide reductase 2. Causes chain termination 3. inhibits cytosine deaminase – breakdown enzyme (S Phase)
PK: Inactivated by cytosine deaminase, Crosses the BBB, Parenteral
USE: *Gemcitibine*: Pancreatic cancer, Hematological/Solid. *Cytarabine:* Hematological ONLY
Resistance: ↑ inactivation (cytosine deaminase), ↓ drug accumulation
SE: Myelosuppression, Neurotoxicity, GI side effects

5. Alkylating agents
MOA: 1. Covalently binds to DNA strands 2. Activation of DNA repair proteins → induction of apoptosis 3. inter/intra-strand crosslinking
Cyclophosphamide – activated by CYP2B, inter/intra-strand crosslinking
USE: CLL, non-Hodgkin's Lymphoma, Breast, Lung, Ovarian CA, immunosuppressant – Nephrotic/nephritic syndrome, vasculitis
SE: hemorrhagic cystitis (Tx: MESNA, fluids), pulmonary toxicity (Tx: steroids), 2º cancers, myelosuppression, alopecia, GI toxicity, SIADH
Resistance: ↓ Activation - CYP2B
Carmustine, Lomustine, bendamustine – inter-strand crosslinking
PK: Parenteral, Wafer, crosses the BBB (lipophilic), eliminated by CO_2/renal
USE: CNS tumors, Lymphoma
Resistance: ↑ alkylguanine-DNA-Alkyltransferase → ↑ increased DNA repair
SE: delayed myelosuppression, delayed pulmonary toxicity (Tx: steroids), 2º cancers, tumor lysis syndrome (allopurinol)
DDI: 6-MP
Cisplatin, Oxaliplatin, Carboplatin - intra-strand crosslinking
USE: Colon CA (FOLF**OX**), Testicular CA, Ovarian CA
Resistance: ↓ influx (copper transporter), ↑efflux (ATP7B), ↑ glutathione,
SE: Renal toxicity (Tx: sodium thiosulfate, mannitol), ototoxicity, peripheral neuropathy
Darcabazine, Procarbazine – activated by liver enzymes
USE: Hodgkin's lymphoma (ABV**D**), Brain tumors,
SE: Disulfiram effects, 2º cancers (leukemia), Myelosuppression, alopecia, teratogenic
Busulfan
USE: CML, CNS tumors
SE: Myelosuppression, alopecia, Delayed Pulmonary fibrosis (fatal), hyperpigmentation



6. Anthracyclines
MOA: 1. DNA intercalation → activation of repair enzymes, 2. Topoisomerase II inhibitors, 3. Generation of ROS (G2 phase)
Doxorubicin, Daunorubicin, Idarubicin, Epirubicin
PK: Does not cross the BBB, Biliary/ Renal elimination – red fluids
USE: Breast CA, Hodgkin's and non-Hodgkin's Lymphoma, Lung CA
Resistance: ↓ Drug accumulation (MDR), ↑ Glutathione, Altered Target
SE: Cardiotoxicity (Tx: Dexrazoxane), Vesicant tissue damage, hand foot syndrome (liposomal formulation),

7. Bleomycin
MOA: Intercalation and Interaction with metals to Generate free radicals → dsDNA breaks (G2 phase)
PK: Inactivated by bleomycin hydrolase (BH), renal excretion
USE: Hodgkin's/Non-Hodgkins Lymphoma, Germ cell tumors
SE: Pulmonary toxicity, skin toxicity, alopecia- **NO myelosuppression**

8. Camptothecans → Topoisomerase I inhibitors
MOA: Prevents Re-ligation of single stranded DNA breaks
Irinotecan – converted to SN-38
topotecan
PK: Cross BBB, SN-38 metabolized by UGT1A1, SN-38 is biliary excretion
Resistance: ↓ Drug accumulation (MDR), Altered Topo I protein
USE: Ovarian CA, Colorectal CA (FOLF**IRI**),
SE: Diarrhea (SN-38), Neutropenia, alopecia

9. Topoisomerase II inhibitors
MOA: Prevents Re-ligation of double stranded DNA breaks
Etoposide, Teniposide
PK: Does not Cross BBB, Renal excretion
USE: Lung CA (CA**E**), solid/hematological malignancies
Resistance: ↓ Drug accumulation (MDR), Altered Topo II protein
SE: Myelosuppression, Alopecia

10. Vinca alkaloids
MOA: Causes Depolymerization of microtubules → blocks mitosis (M phase)
Vincristine, Vinblastine
PK: Fatal if administered intrathecally, does not cross the BBB, Biliary excretion
USE: *Vincristine* – Non-Hodgkin's, Lung CA *Vinblastine* – Hodgkin's lymphoma
Resistance: ↓ Drug accumulation (MDR), Altered tubulin protein
SE: *Vincristine* – Neurotoxicity, Vesicant tissue damage, Tumor lysis syndrome, autonomic dysfunction, *Vinblastine* – Myelosuppression

11. Taxanes
MOA: Causes Polymerization of microtubules → blocks mitosis (M Phase)
Paclitaxel, Docetaxel
PK: Does not cross the BBB, Biliary excretion
USE: Breast CA, Karposi's Sarcoma
Resistance: ↓ Drug accumulation (MDR), Altered Tubulin protein
SE: Myelosuppression, Peripheral neuropathy, alopecia, Hypersensitivity reaction

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