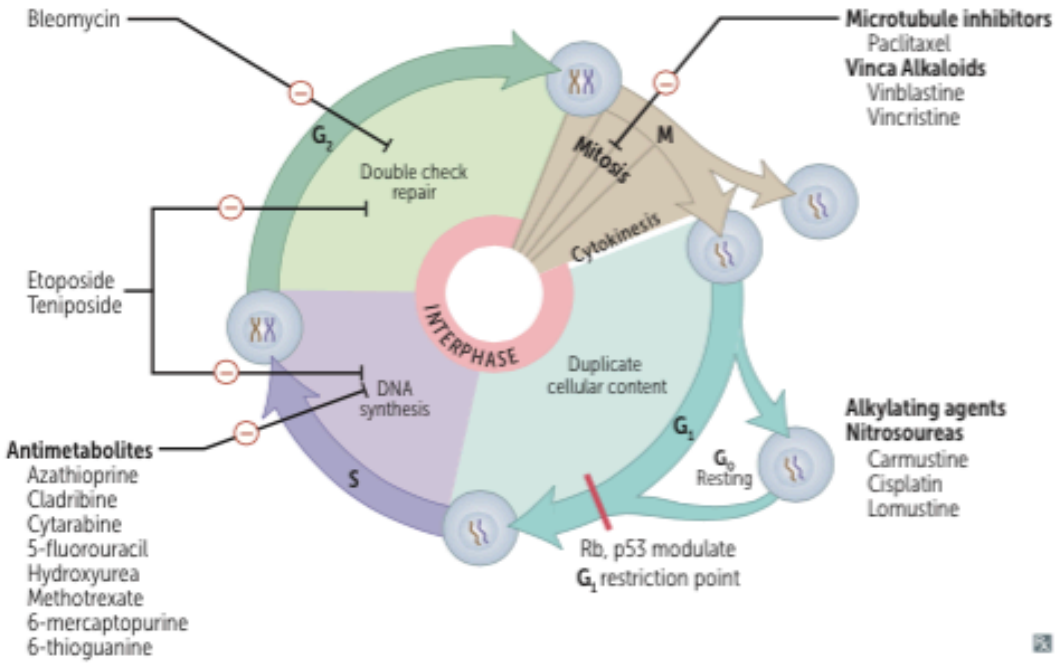
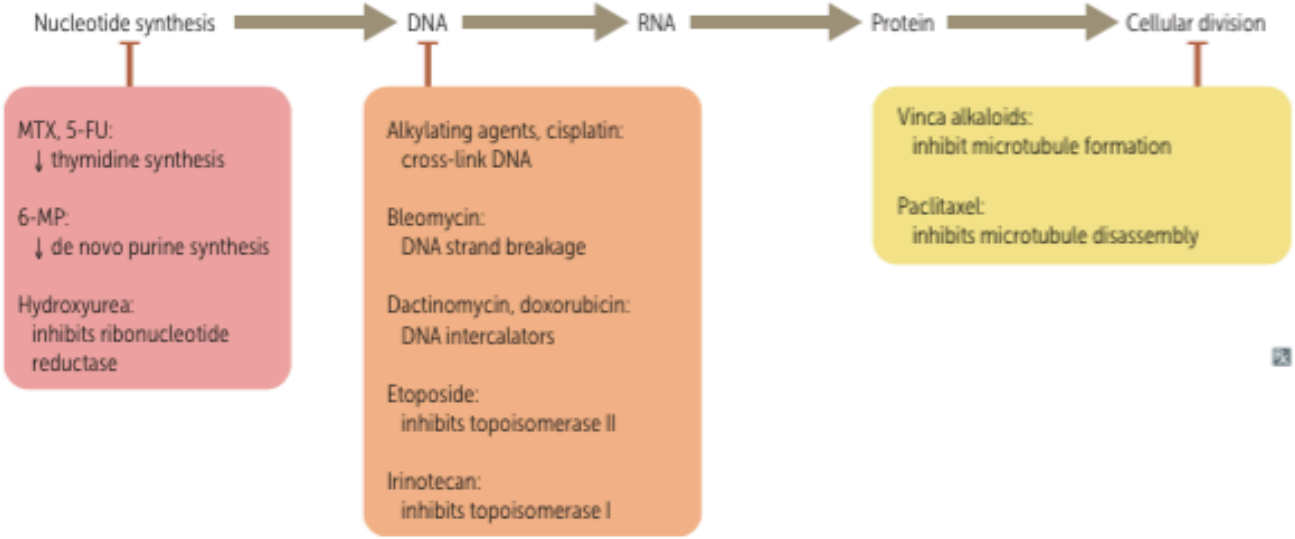
Cancer drugs—cell cycle



Antineoplastics



ALKYLATING AGENTS

DRUG	ACTION/CHARACTERISTICS	INDICATIONS	TOXICITY	RESISTANCE
ALKYLATORS **cell-cycle NON-SPECIFIC**	**Nitrogen-mustard derived agents** **TARGET: N7 POSITION OF GUANINE** ★		Toxicity is worse in cells deficiency in DNA repair enzymes (i.e. **Ataxia telangiectasia**) 1. Bone marrow suppression* occurs 7-10 days post-Rx & recovers 7-10 days later 2. VESICANT 3. Hemorrhagic cystitis 4. Secondary malignancy – AML	
NITROSUREAS **BCNU: Carmustine** **CCNU: Lomustine** **mCCNU: Semustine**	"Non-mustard" alkylators but work similarly **Fat soluble – can cross BBB**	Melanoma, brain tumors	***Prolonged bone marrow suppression (~6 weeks)**	↓intracellular accumulation of the drug **↑intracellular thiol (i.e. Glutathione) concentration – *can neutralize alkylation*** Change in DNA repair enzymes
TEMOZOLOMIDE	Crosses BBB Oral pro-drug dimilar to DTIC	Improves survival in **GLIOMAS** when used with radiation therapy		
CYCLOPHOSPHAMIDE	Well-absorbed orally	Breast cancer, lymphoma, leukemia	MYELOSUPPRESSION, Cardiac	
IFOSFAMIDE		Testicular ca, sarcoma, lung ca	**ACROLEIN** – extremely toxic to the bladder mucosa causing vesicular formation → **HEMORRHAGIC CYSTITIS** ****PREVENT W/ MESNA** ★	
MESNA	2-Mercapto Ethane Sulfonate Sodium Supplies free thiol group, which binds to & inactivates acrolein	Prophylaxis for Ifosfamide & cyclophosphamide-induced hemorrhagic cystitis		

ANTI-METABOLITES: *Inhibition of DNA, RNA, or protein synthesis; contraindicated in pregnancy*

DRUG	ACTION/CHARACTERISTICS	INDICATIONS	TOXICITY	MODE OF RESISTANCE
ANTI-METABOLITES	**Cell-cycle SPECIFIC**	Broad range	Myelosuppression, GI, **mucositis** *↑activity = ↑toxicity*	
METHOTREXATE **ANTI-FOLATE** *Any drug with 'trex' is a DHFR inhibitor*	Competitive antagonist of **Dihydrofolate Reductase (DHFR)** – *inhibits DNA synthesis* More soluble at alkaline pH **Don't not cross BBB** **3rd spacing** – collects in pleural effusions & ascitic fluid leading to slow release mimicking a slow infusion with ↑BM & mucosal toxicity	Choriocarcinoma, ALL, NHL, cutaneous T-cell lymphoma, lung ca, breast ca, intrathecal chemotherapy **LEUCOVORIN (FOLINIC ACID) RESCUE***	**Prolonged bone marrow suppression** Skin rashes, **mucositis** **HEPATOTOICITY** (esp. in pts who take MTX for chronic Psoriasis) Pulmonary toxicity ***FOLINIC ACID DECREASES TOXICITY OF MTX**	↑Production of BHFR ↓Affinity of DHFR for MTX **Cells that can't POLYGLUTAMATE**
5-FU **PYRIMIDINE ANALOG**	5-FU converted to fDUMP fDUMP competes w/ DUMP for Thymidylate Synthetase – ***TS inhibitor*** 5FU incorporates into RNA & acts as false pyrimidine **inhibiting translation**	**COLORECTAL CANCER** ***FOLINIC ACID** **↑EFFECTIVENESS OF 5FU** Breast ca, GI malignancies	**Mainly GI (mucositis)** Myelosuppression Skin: sun sensitivity, venous discoloration	↑Expression of TS (gene amplification) ↓Drug sensitivity of enzyme ↓Activation of 5FU (↓activating kinase/phosphorylase or ↓PRPP secondary to Allopurinol)
CAPECITABINE ★ **PYRIMIDINE ANALOG**	Pro-drug of 5FU – ***TS inhibitor*** Take it orally & in liver it converts to fDUMP		**HAND-FOOT SYNDROME****	
CYTARABINE (ARA-C) **PYRIMIDINE ANALOG**	Cytosine arabinoside **Inhibits DNA polymerase** Inhibits DNA elongation	**AML**	Severe BM suppression, mucositis, Pancreatitis Unusual neurotoxicity – *cerebellar dysfunction*	↑Activity of cytidine deaminase ↓Activity of deoxycytidine kinase ↓Affinity of DNA polymerase for ARA-C ↑Expression of DNA polymerase
GEMCITABINE **PYRIMIDINE ANALOG**	Cytosine analog w/ structural similarities to ARA-C **Inhibits DNA polymerase** Inhibits ribonucleotide reductase	**Pancreatic cancer**		
AZACITIDINE **PYRIMIDINE ANALOG**	**Inhibits DNA methyltransferase** causing hypomethylation of DNA leading to cell death **NOT CELL-CYCLE SPECIFIC**	Myelodysplastic Syndrome		
6-MP & 6-TG **PURINE ANALOG**	Inhibits DNA synthesis via formation of 'fraudulent purine' which incorporate in DNA inhibiting further synthesis via inhibition of PRPP & **HGPRT**	Leukemia	Myelosuppression, Mucositis Diarrhea, Nausea/vomiting, Pancreatitis	↓Affinity for HGPRT ↑Drug degradation (↑Xanthine oxidase)
ALLOPURINOL **PURINE ANALOG** ★	Inhibits **xanthine oxidase**: ↓uric acid & xanthine Inhibits PRPP: ↓de novo purine synthesis ****Xanthine oxidase inhibition = longer drug exposure & ↑activity of 6-MP/6-TG toxicity*** ****Decreases activity of 5-FU (inhibits PRPP)***	Gout	Leads to enhanced cytotoxic effect of purine analogues	
CLADRIBINE ★ **PURINE ANALOG**	Adenosine analog Inhibits **adenosine deaminase**	**CURATIVE IN HAIRY CELL LEUKEMIA**		
HYDROXYUREA **UREA ANALOG**	**Inhibits ribonucleotide reductase** Inhibits DNA synthesis	**Sickle Cell Disease – ↑HbF**	Myelosuppression NVD	Mutation or over-expression of ribonucleotide reductase

NATURALLY OCCURRING AGENTS: *Inhibits cell replication; Derived from fungi (antibiotics);* CELL CYCLE NON-SPECIFIC

DRUG	ACTION/CHARACTERISTICS	INDICATIONS	TOXICITY	MODE OF RESISTANCE
ANTHRACYCLINES **DOXORUBICIN** ★ **DAUNORUBICIN** **IDARUBICIN** **EPIRUBICIN**	Intercalates between base pairs block DNA/RNA synthesis **INHIBITS TOPOISOMERASE 2** → strand breakage Generates **oxygen & hydroxyl free** radicals causing strand breaks & membrane damage	Doxo – NHL, breast ca, sarcomas Dauno – AML Ida – hematologic malignancies Epi – NHL, breast ca, sarcomas	**CARDIAC TOXICITY** – dose-dependent cardiomyopathy ★ (synergistic w/ trastuzumab) ****PREVENTED W/ DEXRAZOXANE** (iron chelator prevents free radicals forming) Bone marrow suppression, alopecia, severe NV, secondary malignancies	MULTI-DRUG RESISTANCE (**MDR**) mediated by **P-GLYCOPROTEIN EFFLUX PUMP**
DACTINOMYCIN	Intercalation Binds at transcription initiation complex ***inhibiting RNA elongation*** by RNA polymerase	**WILM'S TUMOR**	Myelosuppression Severe vesicant	
MITOMYCIN-C	Acts like alkylator causing potent cross-linking Preferntial activity in hypoxic conditions	**Anal cancer** (w/ 5FU + radiation) **Superficial bladder cancer**	**TTP** ★	MDR (P-GLYCOPROTEIN)
BLEOMYCIN	Intercalates DNA & produces strand breaks **PREDOMINANT ACTIVITY IN G2 – DISTRUPTS SYNTHESIS OF COMPONENTS NEED FOR MITOSIS** ****CELL CYCLE SPECIFIC**	Testicular cancer, Hodgkin's, NHL Pleurodesing agent to treat pleural effusions	**Free radicals directly toxic to LUNG: interstitial fibrosis** ★ **Lance Armstrong wouldn't take it*	MDR (P-GLYCOPROTEIN)

NATURALLY OCCURRING AGENTS: *Inhibits cell replication; Derived from plants (plant alkaloids);* CELL CYCLE SPECIFIC

DRUG	ACTION/CHARACTERISTICS	INDICATIONS	TOXICITY	MODE OF RESISTANCE
VINCA ALKALOIDS **VINCRISTINE** **VINBLASTINE** **VINDESINE** **VINRELBINE**	**Spindle inhibitors** Bind to tubulin & cause **depolymerization** of microtubules preventing spindle formation & leading to mitotic arrest	Hodgkin's, NHL, lung ca, gliomas, breast cancer (vinorelbine)	**PERIPHERAL NEUROPATHY** (dose-dependent) – sensory is reversible, but motor is not *Vincristine is not as myelosuppressive*	MDR (P-GLYCOPROTEIN)
TAXANES **PACLITAXEL** **DOCETAXEL** **ABRAXANE** **CABAZITAXEL**	**Spindle inhibitors** Binds to tubulin & **enhances polymerization** preventing spindle dissociation & leading to mitotic arrest	Original indication for ovarian ca Very active in breast ca Active in lung ca	Bone marrow suppression Allergies Myalgias & arthralgias **PERIPHERAL NEUROPATHY** Skin: **BEAU'S LINES** on nails *USE OF **STEROIDS** TO PREVENT ACUTE TOXICITY IS CRITICAL	MDR
PODOPHYLLOTOXIN **ETOPOSIDE** **TENIPOSIDE**	**Inhibits DNA topoisomerase 2** Inhibits DNA & RNA synthesis	Testicular cca, lung ca, NHL	Unpredictable hypotension Myelosuppression	MDR
CAMPTOTHECINS **IRINOTECAN***	**Inhibits DNA topoisomerase 1*** Leads to arrest of DNA replication → cell death	Metastatic colon cancer	**EXCESSIVE DIARRHEA requiring treatment with ATROPINE**	Does NOT appear to be MDR mediated even though natural

MISCELLANEOUS AGENTS

DRUG	ACTION/CHARACTERISTICS	INDICATIONS	TOXICITY	MODE OF RESISTANCE
HEAVY METALS **CISPLATIN** **CARBOPLATIUM** **OXALIPLATINUM**	Can change shape to get to N7 guanine Act of **alkylators** **Cell-cycle NON-specific**	**CISPLATIN IS CURATIVE FOR MOST GERM CELL TUMORS (TESTICULAR CANCER)** ★	**NEUROLOGIC TOXICITY**** **NEPHROTOXICITY** ****PREVENTED W/ AMIFOSTINE** Myelosuppression *Wasting of Mg^{2+} & K^{+}*	MDR ↑Production of intracellular **thiol** ↑DNA repair enzymes
L-ASPARAGINASE	Less availability of asparagine for tumor cells **inhibits tumor protein synthesis** & cell proliferation	Pediatric ALL	Pancreatitis	
ARSENIC TRIOXIDE **METALLOID**	Uncertain... probably apoptosis	**Acute Promyelocytic Leukemia**	Interrupts ATP production leading to multisystem failure	
TRANS RETINOIC ACID	Promotes cell differentiation leading to **apoptosis**	**Acute Promyelocytic Leukemia**	HA, fever, dry sky, flu-like symptoms, infections	
BORTEZOMIB	Inhibits the **proteasome**	Multiple Myeloma Mantle Cell Lymphoma		
THALIDOMIDE **LENALIDOMIDE**	Derived from glutamic acid **Inhibits angiogenesis** by interrupting VEGF ↓BM stromal cell support **Anti-osteoclastic**	Multiple Myeloma	Leads to horrendous birth defects	

ANTI-HORMONAL THERAPY

DRUG	ACTION/CHARACTERISTICS	INDICATIONS	TOXICITY	MODE OF RESISTANCE
TAMOXIFEN ★	SERM Blocks estrogen receptor (ER) in breast cancer cells **(anti-estrogen in breast)**	*Can be used in both pre- & post-menopausal settings*	**Estrogen effects:** **THROMBOEMBOLIC DISEASE** **ENDOMETRIAL CANCER**	Change in expression of ER Mutations of ER Selection of ER(-) cells
AROMATASE INHIBITOR AMINOGLUTETHIMIDE **ANASTROZOLE,** **LETROZOLE, EXEMESTANE**	Blocks synthesis of estrone or estradiol from androstenedione & testosterone, respectively	*Can only be used in **post-menopausal** setting when the adrenal gland is the major source of estrogen precursors*	Toxicity due to estrogen withdrawal: ***osteoporosis**, hot flashes, arthralgias*	
PROGESTINS MEGESTROL MEDROXYPROGESTERONE	Anti-estrogen effects ↓Activity of ER (down-regulation)			
LHRH ANALOGS **LEUPROLIDE** **GOSERILIN**	Pituitary inhibition ↓Pituitary release of LH & FASH due to receptor down-regulation, resulting in ↓estrogen & testosterone production	Prostate > breast cancer	**TRANSIENT "FLARE" EFFECT**	
ANDROGEN-R BLOCKER **FLUTAMIDE** **BICALUTAMIDE** **ENZALUTAMIDE**	Analogous to Tamoxifen		Hot flases, impotence "andropause"	
CORTICOSTEROIDS	MOA mostly unknown	Hodgkin's & NHL Supportive care Anti-nausea Appetite stimulant **Decreases cerebral edema** Co-analgesic	Fluid retention, glucose intoleranece, **proximal myopathy**, insomnia, immunosuppression (*Candidal infection of esophagus*), ↑appetite, skin changes, ulcers	

MONOCLONAL ANTIBODIES

Murine mAb = momab Chimeric mAb = ximab Humanized mAb = zumab Human mAb = mumab

DRUG	ACTION/CHARACTERISTICS	INDICATIONS	TOXICITY	MODE OF RESISTANCE
RITUXIMAB ★	*Makes cancer more visible to immune system* Target is **CD20 found on B-cell lymphomas**	**B cell lymphoma**		
IPILIMUMAB	*Blocks inhibitory signals* **TARGETS CTLA-4**	**METASTATIC melanoma**		
★ TRASTUZUMAB	Target is **EGFR**	**Her2/neu+ breast cancer**	**CARDIAC TOXCITY** (reversible)	
CETUXIMAB	*Blocks growth signals* Target is **EGFR**	Squamous cell H&N cancer **WILD-TYPE k-ras colon cancer**	**SKIN RASH (Acneiform Eruption)** indicating appropriate target has been inhibited is difficult to treat	
BEVACIZAMAB	*Stops new blood vessels from forming* Target is **VEGF**	Colon cancer Refractory gliomas	**WOUND HEALING** ★	

SIGNAL TRANSDUCTION INHIBITORS: Cell Surface Receptor Associated Tyrosine Kinase Inhibitors (TKI)

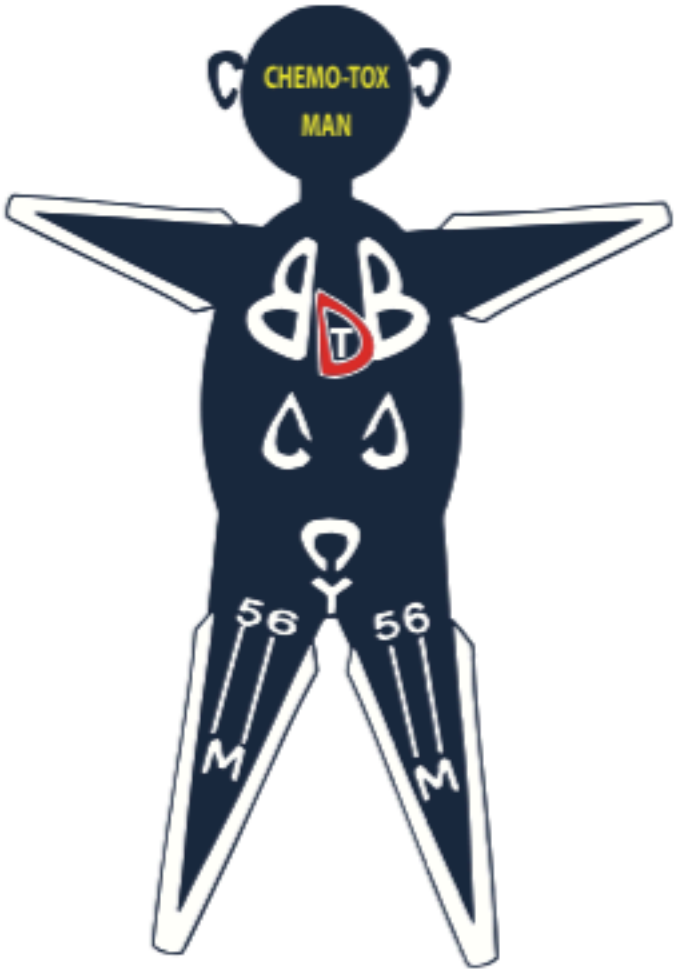
DRUG	ACTION/CHARACTERISTICS	INDICATIONS	TOXICITY	MODE OF RESISTANCE
LAPATINIB	Targets EGFR: Her-2 domain (ErbB-2)	Breast cancer		
GEFITINIB **ERLOTINIB**	Targets EGFR: non-Her-2 domain	Lung cancer		
SUNITINIB	Targets VEGF	Renal cell carcinoma		
SORAFINIB	Target VEGF	Hepatoma		

SIGNAL TRANSDUCTION INHIBITORS: NON-Cell Surface Receptor Associated Tyrosine Kinase Inhibitors (TKI)

DRUG	ACTION/CHARACTERISTICS	INDICATIONS	TOXICITY	MODE OF RESISTANCE
★ IMATINIB	Targets **BCR-ABL** oncogene Inhibits TK activity of the oncogene	**CML** GI stromal tumors (**c-kit**)	Diarrhea, **MYALGIAS**, Fluid retention	Mutation of the BCR-ABL gene
VEMURAFENIB	Inhibits mutated BRAF protein kinase Inhibits RAS pathway	Metastatic Melanoma	Arthralgias, fatigue, rash Cutaneous squamous cell carcinoma	
M-TOR INHIBITORS *"olimus"*	Inhibit tumor growth	Renal cell cancer		

DRUG	ACTION/CHARACTERISTICS	INDICATIONS	TOXICITY	MODE OF RESISTANCE
INTERFERON	Interfere with viral replication	Melanoma, hairy cell leukemia, T-cell lymphoma, early stage CML	FLU-LIKE SYMPTOMS Myelosuppression, Hepatotoxicity	

Common chemotoxicities



Cisplatin/**C**arboplatin → acoustic nerve damage (and nephrotoxicity)

Vincristine → peripheral neuropathy
Bleomycin, **B**usulfan → pulmonary fibrosis
Doxorubicin → cardiotoxicity
Trastuzumab → cardiotoxicity
Cisplatin/**C**arboplatin → nephrotoxic (and acoustic nerve damage)

CYclophosphamide → hemorrhagic cystitis

5-FU → myelosuppression
6-MP → myelosuppression

Methotrexate → myelosuppression