CANCER PHARMACOLOGY I

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Objectives

- Describe the mechanism of action and pharmacology of chemotherapy agents and targeted therapies used for the treatment of hematologic and solid tumor malignancies
- Identify the need for dose adjustments of cancer therapies based on organ dysfunction
- Recognize common and unique adverse drug reactions of cancer therapies and associated prevention and management strategies

CELL CYCLE NONSPECIFIC AGENTS

M Phase Specific

Antimicrotubule Agents

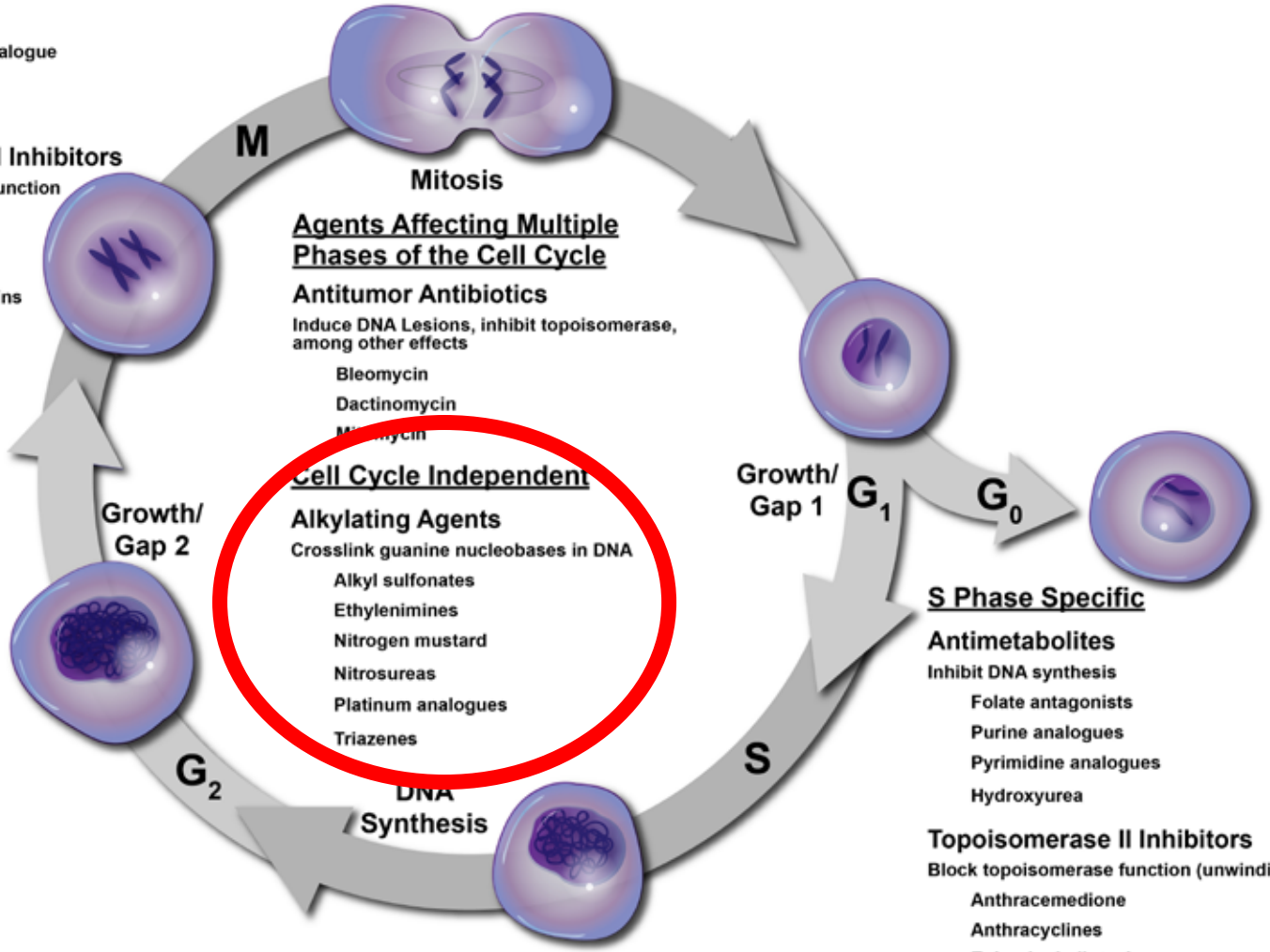
Inhibit function of microtubules

- Epothilones
- Halichondrin B analogue
- Taxanes
- Vinca alkaloids

Topoisomerase II Inhibitors

Block topoisomerase function (unwinding DNA)

- Anthracemedione
- Anthracyclines
- Epipodophyllotoxins



Agents Affecting Multiple Phases of the Cell Cycle

Antitumor Antibiotics

Induce DNA Lesions, inhibit topoisomerase, among other effects

- Bleomycin
- Dactinomycin
- [illegible]ycin

Cell Cycle Independent

Alkylating Agents

Crosslink guanine nucleobases in DNA

- Alkyl sulfonates
- Ethylenimines
- Nitrogen mustard
- Nitrosureas
- Platinum analogues
- Triazenes

S Phase Specific

Antimetabolites

Inhibit DNA synthesis

- Folate antagonists
- Purine analogues
- Pyrimidine analogues
- Hydroxyurea

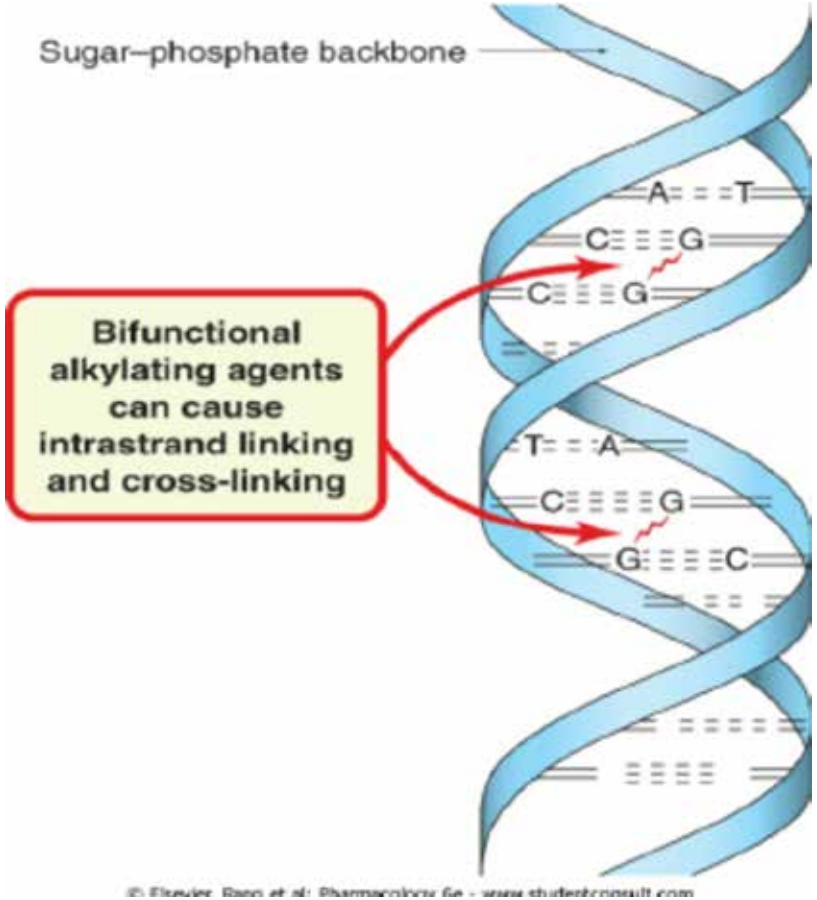
Topoisomerase II Inhibitors

Block topoisomerase function (unwinding DNA)

- Anthracemedione
- Anthracyclines
- Epipodophyllotoxins

Class	Chemotherapy Agent
Alkylating Agents (Classical)	
Nitrogen mustards	Bendamustine (Bendeka) Cyclophosphamide (Cytoxan) Ifosfamide (Ifex) Melphalan (L-phenylalanine; Alkeran, Evomela) Mechlorethamine (Mustargen) Chlorambucil (Leukeran)
Alkyl sulfonate	Busulfan (Myleran)
Aziridines	Mitomycin C (Mutamycin) Thiotepa (Thioplex)
Nitrosoureas	Carmustine (BCNU; Bicnu) Lomustine (CCNU; Ceenu)
Alkylating Agents (Non-Classical)	
Triazenes	Dacarbazine (DTIC; DTIC-Dome) Procarbazine (Matulane)
Hydrazines	Temozolamide (Temodar)
Miscellaneous	Trabectedin (Yondelis)

Alkylating Agents



https://www.researchgate.net/figure/The-effects-of-bifunctional-alkylating-agents-on-DNA-Note-the-cross-linking-of-two_fig1_221920821

Alkylating Agents: Class Toxicities

- Infertility: Oligospermia, amenorrhea
- Teratogenic: exposure in 1st trimester associated with increased risk of fetal malformations
  - Therapy in 2nd or 3rd trimester not associated w/ increased risk
- Carcinogenic
  - Melphalan >> cyclophosphamide/ifosfamide
  - Highest risk 5-10 years after exposure (MDS/AML)
  - Increased risk of bladder cancer from cyclophosphamide

Nitrogen Mustard

	Cyclophosphamide	Ifosfamide
Common uses	Breast, lymphoma, leukemia, sarcoma, HSCT, immunosuppressive tx	Sarcoma, lymphoma, testicular
Dosing	PO: 500-300mg/m^2 IV: 250-2000mg/m^2; 60-100mg/kg	IV: 1-5g/m^2/d
Common Toxicities	Myelosuppression (platelet sparing) Delayed nausea/vomiting (dose-related) Alopecia	
Rare/ Serious Toxicities	**Hemorrhagic cystitis**	
	Cardiotoxicity w/ high dose Interstitial pneumonitis SIADH	Fanconi's syndrome **Encephalopathy** (treat with methylene blue)
Notes	Drug-drug interaction with warfarin – monitor PT/INR **Dose reduce for renal dysfunction**	
	Uroprotection with mesna (Doses >1500-2000mg/m^2)	Uroprotection with mesna **ALWAYS** (60% of total ifos dose given pre and post infusion)

Alkyl Sulfonate: Busulfan

- **ADEs**
  - Severe myelosuppression (myeloid >lymphoid)
- **High dose (HSCT)**
  - Pharmacokinetic targeted dosing
  - Seizures: Pre-med with anticonvulsant
  - Hepatic sinusoidal obstruction syndrome (formerly venoocclusive disease
  - “Busulfan lung” (with chronic use)
  - “Busulfan tan” (skin hyperpigmentation)

https://www.seattlecca.org/healthcare-professionals/clinical-labs/busulfan-lab-pharmacokinetics-lab

Nitrosoureas: Carmustine, Lomustine

- **Common Uses**: Brain tumors, HSCT
- Highly lipophilic, crosses blood-brain barrier
  - CNS > 50% of plasma concentration
- **Major Toxicities**: Myelosuppression and pulmonary
  - Cycles at least 6 weeks apart due to delayed & prolonged myelosuppression
    - Neutrophil recovery in ~ 6 weeks, platelet recovery in ~ 4 weeks
  - Pulmonary function tests at baseline and periodically during therapy
    - Increased risk of pulmonary toxicity if baseline FVC or DL_{CO} < 70% of predicted
- **Dose Reductions**: Renal dysfunction

Triazenes: Procarbazine, Dacarbazine

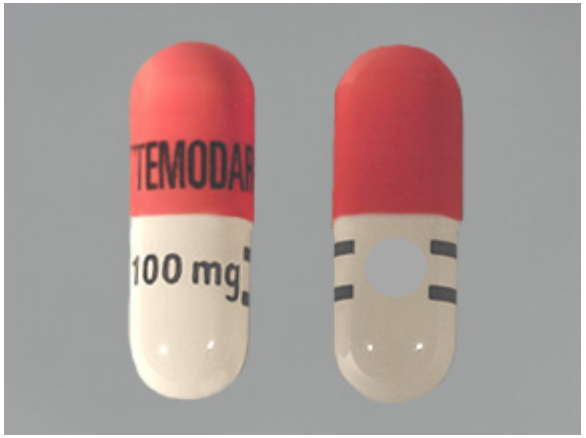
- **Common Uses**: Lymphomas, brain tumors, pheochromocytoma (dacarbazine)

- **Major Toxicities**: Highly emetogenic, bone marrow suppression

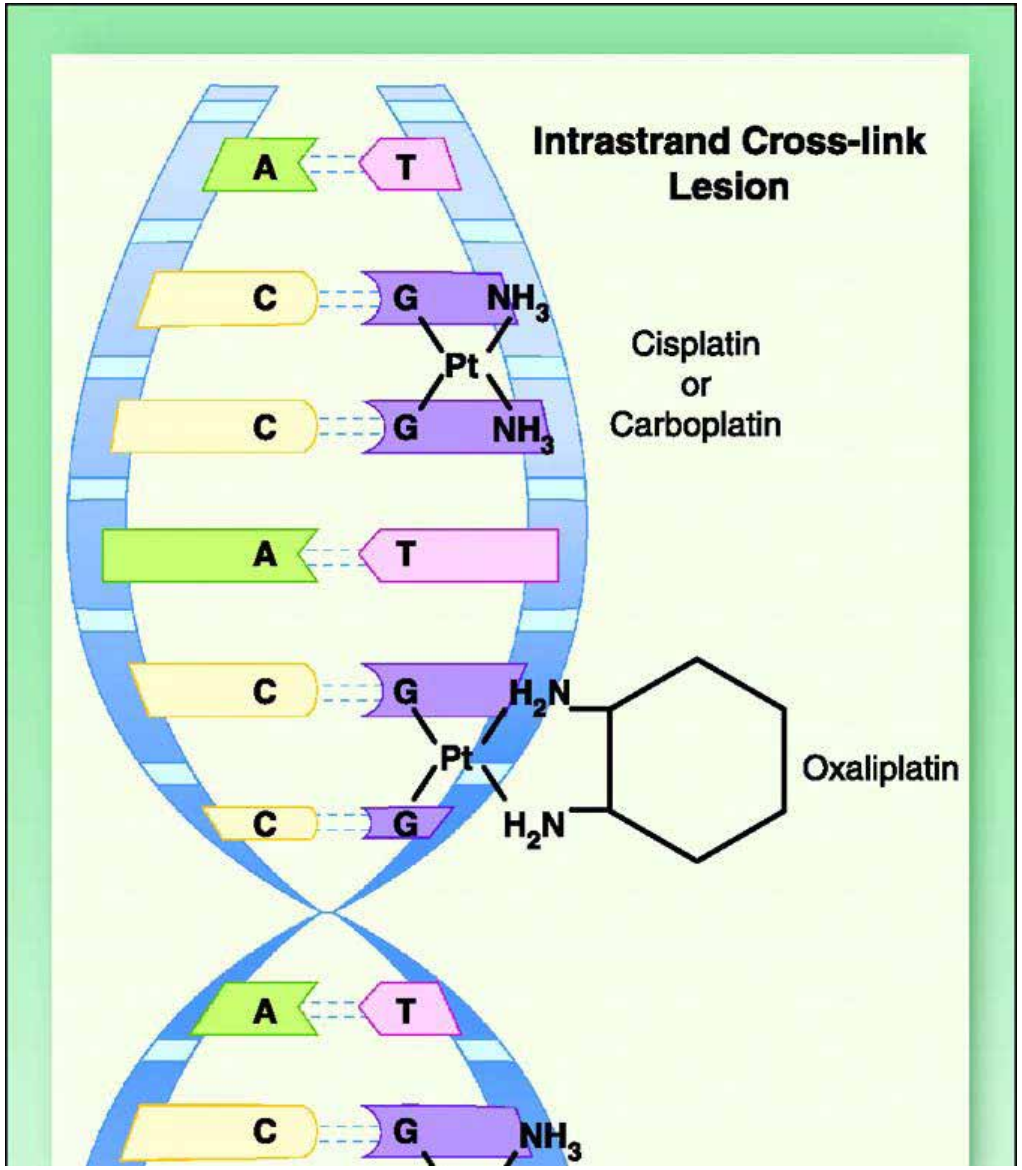
- Procarbazine: a monoamine oxidase inhibitor (MAOI)
  - Potentiates other CNS drugs (barbiturates, opiates, antihistamines)
  - Hypertensive reactions w/ other sympathomimetics, TCAs, or tyramine-containing foods
  - Interaction with alcohol: disulfiram-like effect (sweating, flushing, headache)

Hydrazine: Temozolamide

- **Origin**: Analogue of dacarbazine, inactive in parent form
  - Crosses BBB & does not require liver for activation
- **Common Uses**: Brain tumors/with XRT, and melanoma
  - Given 5 days Q28 days or ½ dose continuously with XRT
- **Major Toxicities**:
  - Myelosuppression (anemia uncommon)
  - Lymphopenia–*PJP* (*PCP*) prophylaxis when given with XRT
  - Moderate nausea/vomiting (take at night), anorexia, flu-like sxs
  - Photosensitivity



Platinum Agents



Teicher BA. *Clin Cancer Res.* 2008.

Platinum Agents: Dosing

	Cisplatin	Carboplatin	Oxaliplatin
Common Uses	Broad spectrum activity against numerous malignancies		
Dosing	Up to 100 mg/m^2 Q21 days (50-75 mg/m^2 when used in doublet regimens) Weekly with XRT	<u>Calvert Equation</u>: Dose (mg) = AUC x (GFR* + 25) NCI recommends dose cap with max CrCl 125 mL/min	85-130 mg/m^2 Q2-3 weeks
Notes	Excreted in urine **50% dose reduction for CrCl <60 ml/min** (or split dosing)	Can give in HD	Rapid and extensive nonenzymatic metabolism

Platinum Agents: Variations in Toxicity

Cisplatin	Carboplatin	Oxaliplatin

• **Severe N/V**, acute, delayed
• **Renal dysfunction**
• Electrolyte wasting
• Peripheral Neuropathy
• Reduces clearance of other drugs (give other drug first)
• **Ototoxicity/tinnitus**, high frequency hearing loss (cumulative, irreversible)
• SIADH
	• Moderate-severe N/V
	• Peripheral neuropathy
	• **Myelosuppression** (thrombocytopenia)
	• **Hypersensitivity reaction** after dose 7-9 (can desensitize)
		• **Neuropathy**, acute & chronic (sensory/ peripheral, dose limiting)
		  • *Acute*: Triggered by cold
		  • Laryngo-pharyngeal dysesthesias with choking sensation
		• Dose-dependent neurotoxicity, typically >850mg/m^2 (reversible)

Anthracyclines

- **Drugs**: Doxorubicin/liposomal doxorubicin, daunorubicin, idarubicin, epirubicin, valrubicin, mitoxantrone
- **Mechanism**: Inhibit DNA & RNA synthesis
  - Intercalate between DNA, single and double strand breaks
  - Free radical formation → iron-anthracycline complexes bind to DNA
  - Also Topoisomerase II inhibitor
- Antitumor activity related to AUC rather than peak drug levels; administered by variety of schedules
- Metabolized in liver to active species; 40-50% of drug excreted in stool
  - **Dose reduction required for liver dysfunction** (especially with Tbili)

Anthracycline General Toxicities

- Myelosuppression: Dose-limiting neutropenia
- GI: Mucositis, N/V, diarrhea
- Alopecia
- Discoloration of bodily fluids
- Radiation recall
- Vesicant: Severe tissue damage
  - Use dexrazoxane as an antidote

Anthracycline Cardiotoxicity

- Caused by free radical damage to myocardium
- Risk factors: Bolus dosing, age, previous chest XRT, cardiac disease, HTN, concomitant chemotherapy (taxanes, cyclophosphamide, trastuzumab)
- Baseline LVEF and every 3-6 months
  - Use cautiously/avoid if LVEF < 50%
- Cardioprotectant: Dexrazoxane (controversial use)

Cumulative Dose (Doxorubicin)	Risk
< 400 mg/m^2	0.14%
500-550 mg/m^2	4%
550-600 mg/m^2	18%
> 600 mg/m^2	36%

Misc. Cell Cycle Nonspecific Agents

Class	Chemotherapy Agent
Biologic agents & other	Interferon Trabectedin mTOR inhibitors Interleukin-2 (Aldesleukin) Arsenic trioxide (Trisenox) All-*trans* retinoic acid (ATRA) Omacetaxine (Synribo) Talimogene laherparepvec (TVEC, Imlygic)

Trabectedin (Yondelis)

- **Origin**: Marine-derived alkylating agent
- **Common Uses**: Soft tissue sarcomas
- **Mechanism**: Alkylating agent, blocking cell cycle progression due to alteration of DNA transcription
- Given as 24-hr infusion (outpatient pump)
  - Pre-med with dexamethasone 20 mg IV 30 min before each infusion
- **Major Toxicities**:
  - Myelosuppression
  - Increased LFTs
  - Increased creatine phosphokinase (CPK)
  - Fatigue, hand-foot syndrome, N/V/D
  - Cardiac: LVEF at baseline and every 2-3 months

mTOR Inhibitors

- **Common Uses**:
  - Temsirolimus: Renal Cell Carcinoma (RCC)
  - Everolimus: Breast Cancer, uterine cancer, PNET, RCC
- **Mechanism**: Inhibitors of mechanistic (mammalian) target of rapamycin
  - Suppresses hypoxia-mediated angiogenesis and endothelial cell proliferation by reduced production of VEGF
- **Major Toxicities**:
  - Metabolic disturbances (hyperglycemia, hyperlipidemia)
  - Myelosuppression
  - Temsirolimus: Infusion reactions (pre-med with antihistamine)
  - Everolimus: Mucositis/stomatitis

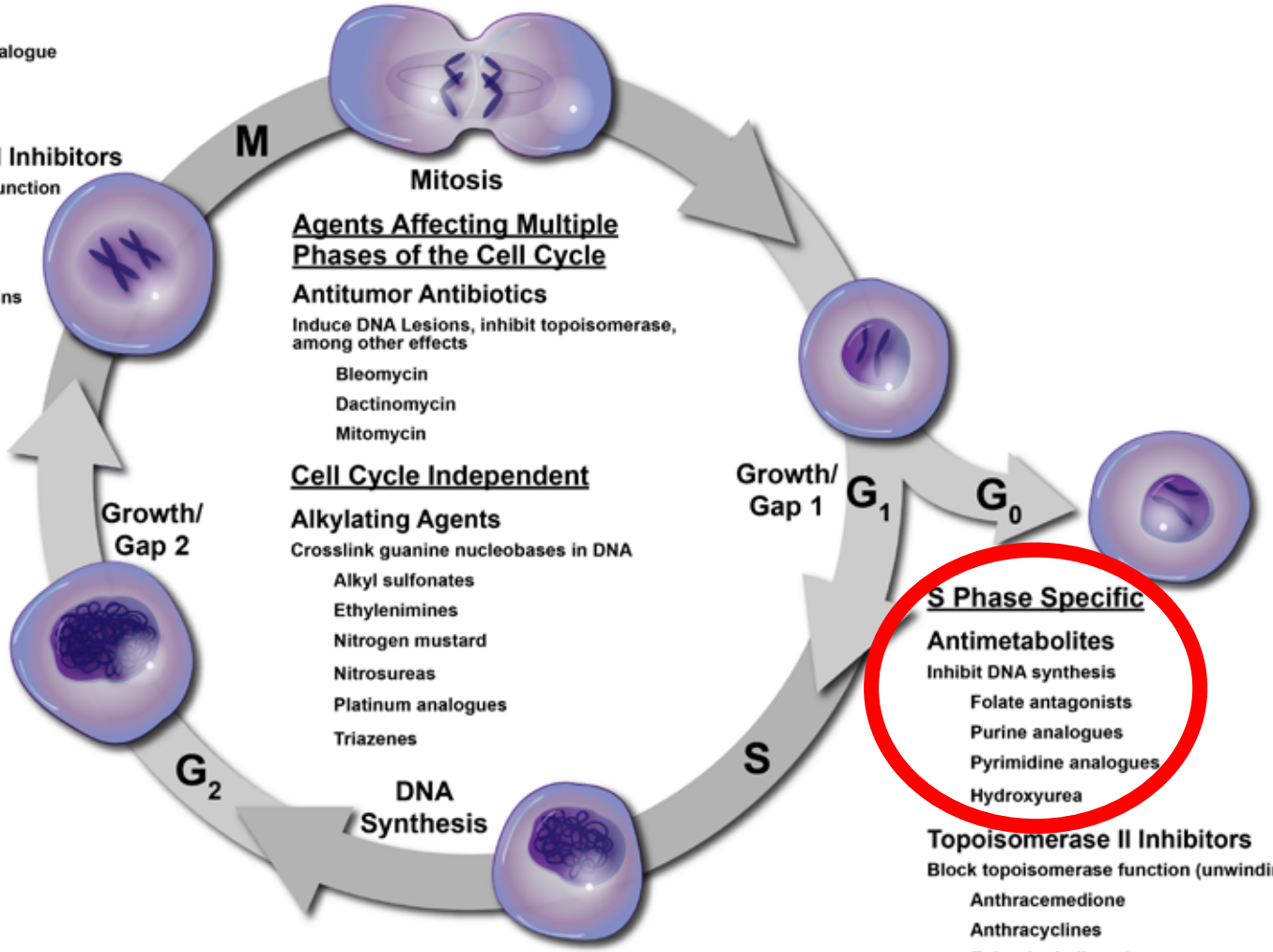
Aldesleukin (Interleukin-2; IL-2)

- **Uses**: RCC, melanoma
- **Mechanism**: Enhances lymphocyte mitogenesis and cytotoxicity, induces LAK and NK activity
- **Dose**: 600,000 units/kg Q8H for up to 14 doses; repeat after 9 days
- **Common Toxicities**:
  - Capillary leak syndrome – **dose-limiting toxicity** (hypotension)
  - Constitutional symptoms: Chills, fever, malaise
  - N/V, diarrhea, stomatitis
  - Acute liver and renal toxicity
  - Arrhythmias (Afib, Vtach)

Arsenic Trioxide

- **Common Uses:** APL (with all-trans retinoic acid)
- **Mechanism**: Induces damage and degradation of fusion protein PML/RARα
  - Direct antiproliferative activity via cell cycle arrest; inhibits angiogenesis; induces apoptosis
- **Major Toxicities**: APL differentiation syndrome
  - Fever, dyspnea, acute respiratory distress, weight gain, pulmonary infiltrates, pleural/pericardial effusions, edema, leukocytosis, multiorgan failure (usually in 1st month)
  - Treat with high-dose steroids
- **Other Toxicities**:
  - QTc prolongation (> 500msec); Baseline EKG and weekly
  - Fatigue, dizziness, headache, peripheral neuropathy
- **Use cautiously in renal insufficiency** (CrCl < 30mL/min)

CELL CYCLE SPECIFIC AGENTS



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- Mitomycin

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- Nitrosureas
- Platinum analogues
- Triazenes

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Antimetabolites

Inhibit DNA synthesis

- Folate antagonists
- Purine analogues
- Pyrimidine analogues
- Hydroxyurea

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Antimetabolites: Folate Antagonists

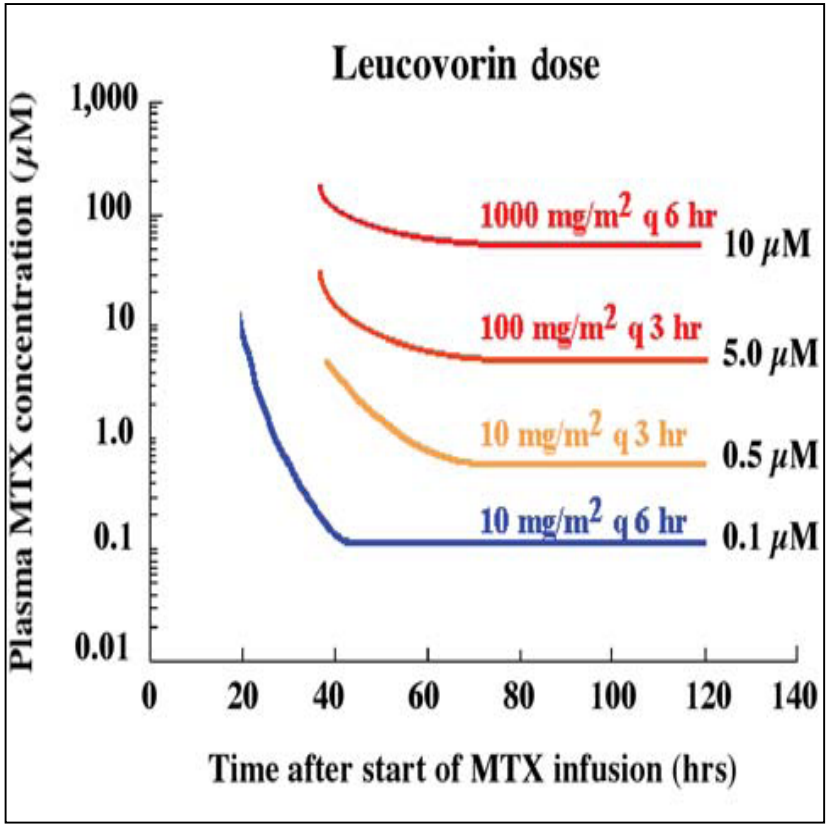
- **Mechanism** (S phase):
  - Actively transported into cell by transport proteins, metabolized to polyglutamated forms to exert cytotoxic effects
  - Inhibits dihydrofolate reductase (DHFR) = Causes depletion of intracellular reduced folate essential for thymidylate and purine synthesis
- **Drugs**: Methotrexate, Pemetrexed, Pralatrexate
- **Common Uses**: Various solid and hematologic tumors

Methotrexate

- Most widely used antifolate in cancer chemotherapy
- Penetrates and exits slowly from third-space fluids
  - Prolonged half-life of drug, leading to increased myelosuppression
- **Elimination**: Mainly renal
  - Avoid: NSAIDs, penicillins, cephalosporins, probenecid, sulfamethoxazole/trimethoprim
- **Dose reduction required in renal dysfunction**
  - Adequate hydration is key
- High-dose (>1g/m^2) therapeutic concentrations in CSF
- Intrathecal may result in myelosuppression and/or mucositis as detectable serum levels may be achieved

Methotrexate: High-Dose Therapy

- Doses ≥500 mg/m^2 require leucovorin rescue, started 24hr after start of infusion and until <0.05 micromolar
- Aggressive IV hydration with urine alkalinization (PO or IV sodium bicarbonate) prior to therapy and until drug clearance



Adapted from Bleyer WA. In: Baer DM, Dita WR, eds. c1981 American Society of Clinical Pathologists.

Methotrexate: ADEs

- **Dose-Limiting**: Myelosuppression
- Mucositis ~ 3-7 days after therapy
- Nephrotoxicity
  - Intratubular precipitation, direct toxic effects on renal tubules
- Hepatotoxicity: Acute and chronic
- Pneumonitis: Fevers, cough, interstitial pulmonary infiltrates
- Neurotoxicity with high-dose
  - Acute and chronic encephalopathy
- Neurotoxicity with intrathecal administration

- Can use glucarpidase in patients who fail to clear

Pemetrexed (Alimta)

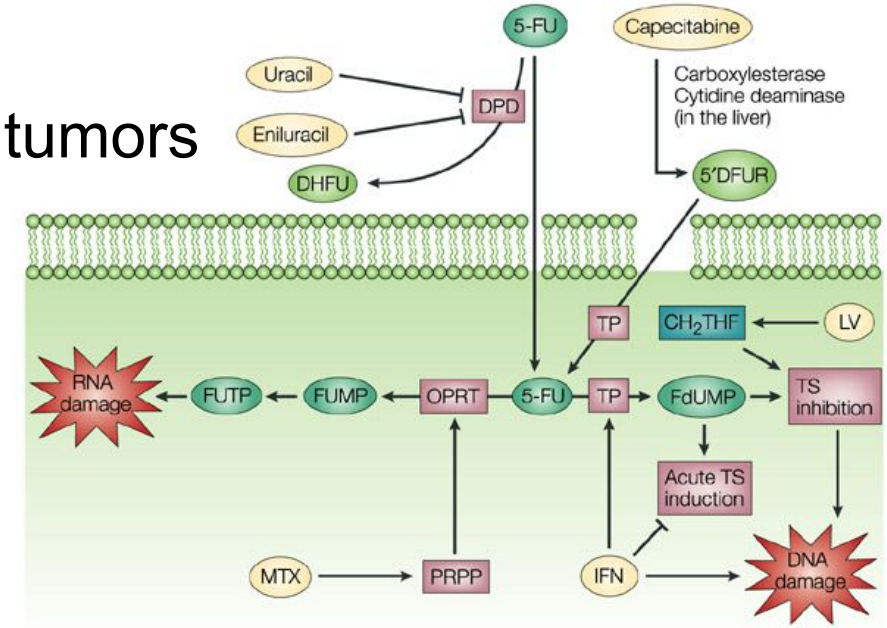
- **Common Uses**: Solid tumors
- **Elimination**: Mainly renal excretion
  - Same drug interactions as methotrexate (avoid NSAIDs)
  - **Dose reduction for renal dysfunction**
    - Not recommended if CrCl <45 mL/min
- **Major Toxicities**:
  - Myelosuppression
  - Generalized pruritic, painful rash
    - Dexamethasone 4mg BID x 3 days (day before, day of, and day after)
- Provide vitamin supplementation
  - Folic acid (400-1000 mcg) daily (start 5 days prior and continue at least 12 days after last dose)
  - Cyanocobalamin (B12) 1000mcg IM Q8-10 weeks

Pralatrexate

- **Common Uses**: Relapsed/refractory peripheral T-cell lymphoma
- Similar to methotrexate/pemetrexed
  - Mainly renal excretion
  - Use with caution in renal dysfunction
  - Same drug interactions as methotrexate
- Replenish with folic acid 1-1.25 mg daily and B12 1000mcg IM Q8-10 weeks to reduce toxicities
- Same toxicity profile as methotrexate and pemetrexed

Antimetabolites: Fluorinated Pyrimidines

- **Drugs**: Fluorouracil, capecitabine, trifluridine/tipiracil
- **Mechanism**:
  - Incorporated into RNA and DNA
  - Direct inhibitors of thymidine nucleotides via inhibition of TS by the 5-FU metabolite FdUMP
- **Common Uses**: Multiple solid tumors



Nature Reviews | Cancer

5-Fluorouracil (5-FU)

- **Dosing**:
  - IV push or continuous infusion
  - Dose reduction considered with hepatic dysfunction

- **Elimination**:
  - >80-85% metabolic conversion by dihydropyrimidine dehydrogenase (DPD), widely present outside of hepatic tissues
  - 3-5% of patients have DPD deficiency, leading to increased toxicity

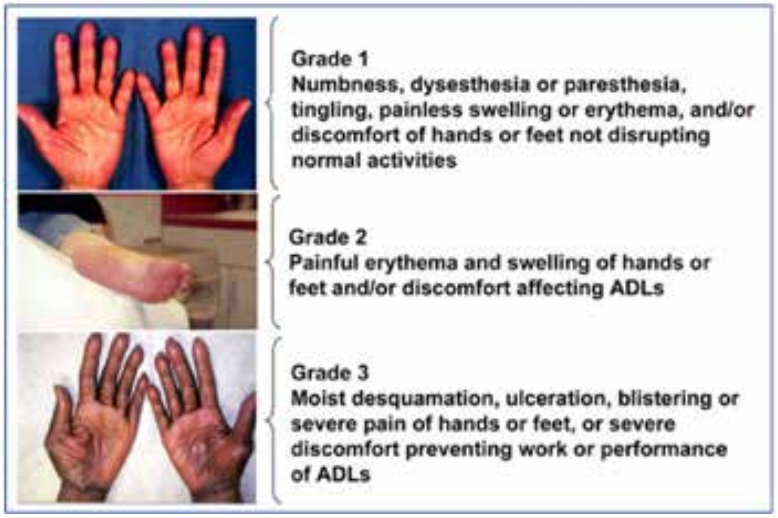
- Leucovorin increases efficacy by optimizing binding to TS

5-Fluorouracil: Toxicities

Bolus dosing	Continuous infusion
Myelosuppression (dose limiting)	Mucositis
	Diarrhea
	Hand foot syndrome (HFS/PPE)
	Myocardial ischemia

- Alopecia, hyperpigmentation, photosensitivity, ocular toxicity, N/V, cerebellar ataxia
- Uridine triacetate (Vistogard) as antidote for overdose or early onset toxicity (ie. DPD deficiency)

Capecitabine (Xeloda)



- Oral prodrug of 5-FU
  - Conversion to 5-FU in the tumor by thymidine phosphorylase
- **Dosing**:
  - 2 weeks on then 1 week off
    - Mimics continuous infusion 5FU toxicities (HFS, diarrhea)
    - HFS (onset ~2-3 months): prevention with moisturizers, lifestyle changes
  - Increased toxicity in renal dysfunction
    - Reduce dose by 25% with CrCl 30-50 mL/min
    - Contraindicated if CrCl < 30 mL/min
- **DDIs**:
  - Black box warning with warfarin – significant increases in PT/INR
  - Increased phenytoin toxicity with taken concurrently

Trifluridine/Tipiricil (Lonsurf)

- **Indication**:
  - Metastatic colon cancer after previous therapy
- **Dosing**:
  - Max 80 mg/dose given BID (based on Trifluidine component) days 1-5 and 8-12 Q28 days, with food (calendar needed for patients)
- **Toxicities**:
  - Neutropenia, thrombocytopenia (check CBC days 1 and 15 each cycle)
  - N/V/D, abdominal pain
  - Weakness, fatigue, fever

Antimetabolites: Other Pyrimidine Analogs

- **Drugs**: Cytarabine, Gemcitabine
- **Common Uses**: Multiple solid and hematologic cancers
- **Mechanism** (S phase):
  - Transports across cell membrane → phosphorylated to active triphosphate form within tumor cells → incorporated into RNA/DNA → inhibits DNA synthesis

Cytarabine: Toxicities

Conventional Dose continuous infusion (100-200 mg/m^2)

- **N/V, diarrhea**
- Alopecia
- Neutropenia & thrombocytopenia
- Rash
- Increased LFTs
- **"Ara-C syndrome"**

High-Dose bolus (1-3 g/m^2)

- Severe myelosuppression
- Mucositis
- **Cerebral & cerebellar dysfunction**: slurred speech, ataxia, confusion, coma (daily assessment of mental status)
- Pulmonary toxicities (noncardiogenic pulmonary edema)
- Hand-foot syndrome
- **Conjunctivitis** (ophthalmic corticosteroids)

Hypomethylating Agents

- **Drugs**: Azacitidine (Vidaza), Decitabine (Dacogen)
- **Common Uses**: Hematologic malignancies
  - IV and SQ dosing for Azacitidine
- **Mechanism**:
  - Inhibition of DNA methyltransferase, causes hypomethylation and apoptosis
  - Restores normal function of genes essential for cellular proliferation and growth
- **Toxicities**:
  - Myelosuppression (DAC >> AZA)
  - Fevers
  - Fatigue
  - Nausea/vomiting

Antimetabolites: Purine Analogs

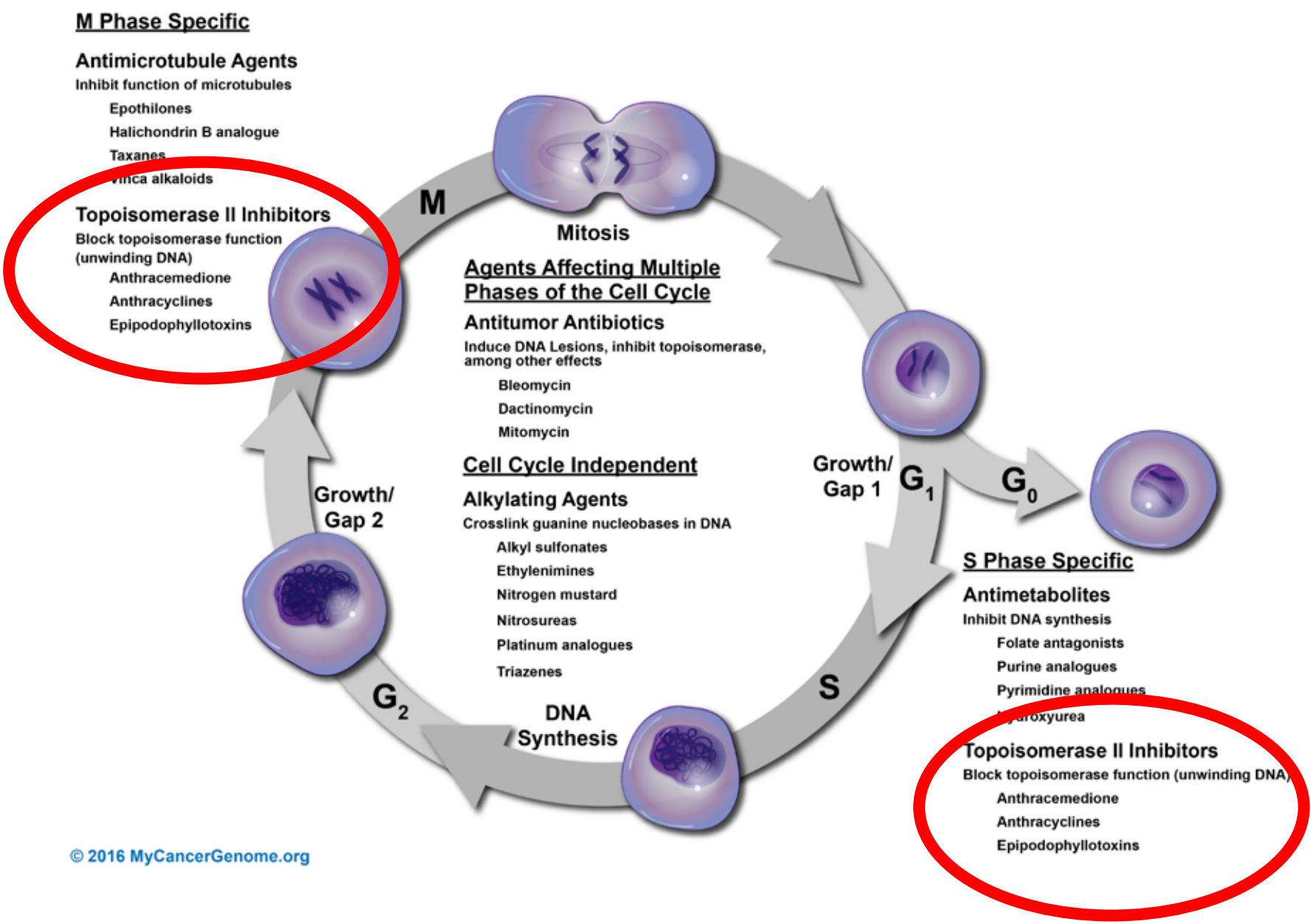
Class	Chemotherapy Agent
Purine Analogs	Mercaptopurine (6-MP) Thioguanine (6-TG) Fludarabine (Fludara) Cladribine (2-CdA) Pentostatin (Nipent) Clofarabine (Clolar) Nelarabine (Arranon)

Purine Analogs

- **Drugs**: 6-mercaptopurine (6MP) and 6-thioguanine (6TG)
- **Common Uses**: Acute leukemias
- **Mechanism**:
  - Incorporates thiopurine nucleotides into DNA & RNA → inhibition of DNA synthesis and function & RNA processing and/or mRNA translation
- **Genetics and 6MP/6TG**:
  - Thiopurine S-methyltransferase (TPMT)
  - Nudix hydrolase 15 (NUDT15)
  - Heterozygous deficiency = 30-70% of dose
  - Homozygous deficiency = 10% of dose

Fludarabine

- **Common Uses**: Lymphoid (CLL, low-grade NHL), other hematologic cancer
- Renally eliminated
  - Reduce dose for CrCl <70mL/min
  - Not recommended if CrCl < 30mL/min
- **Toxicities**:
  - Myelosuppression- Neutropenia, thrombocytopenia
  - Prolonged nadir and recovery may occur
    - CD4 and CD8 T-cells may take >1 yr to recover
    - Increased risk of opportunistic infections, e.g., herpes, fungal, PCP pneumonia (consider PCP prophylaxis)
  - Autoimmune hemolytic anemia
  - Mild and transient elevation in LFTs
  - Neurotoxicity

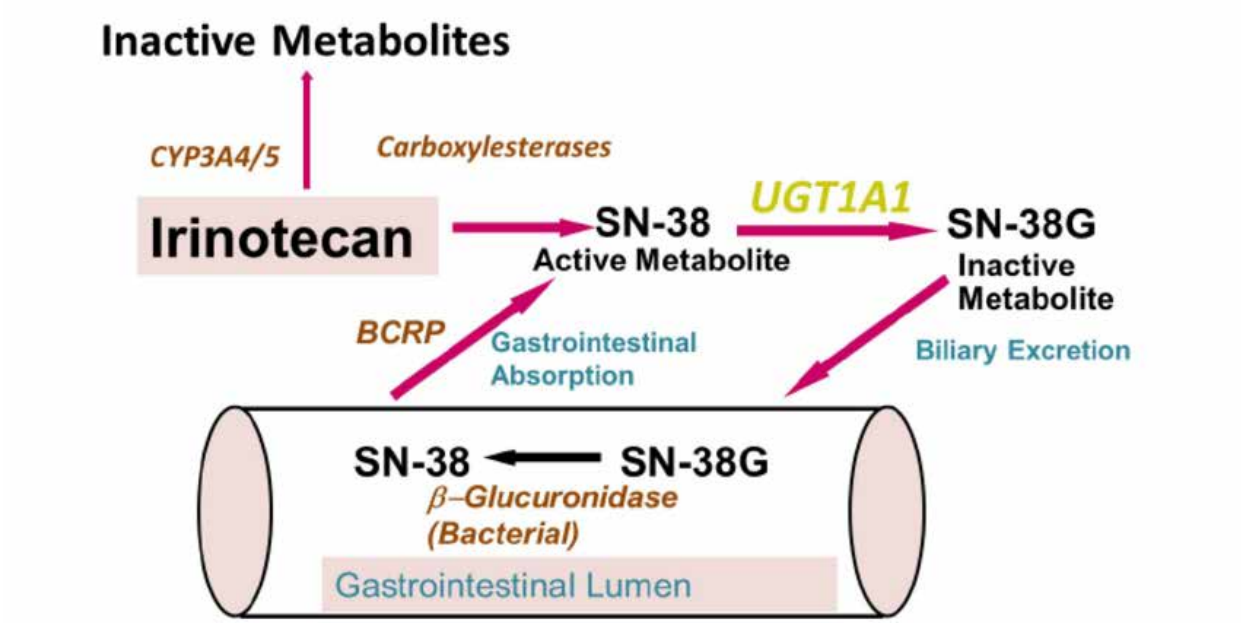


Topoisomerase I Inhibitors

- **Drugs**: Irinotecan, topotecan
- **Mechanism** (S phase):
  - Stabilize topo-I-DNA complex, preventing release of the enzyme
  - Collision of this complex with the replication fork causes double-strand DNA break → cell cycle arrest, apoptosis
- **Toxicities**:
  - Myelosuppression (neutropenia)
  - Alopecia
  - Stomatitis
  - N/V
  - Diarrhea (Irinotecan)
    - Acute (<24 hours): Cholinergic, **treat with atropine**
    - Delayed (>24 hours): Direct irritation of GI mucosa by SN-38, **treat with loperamide**

Irinotecan and SN-38

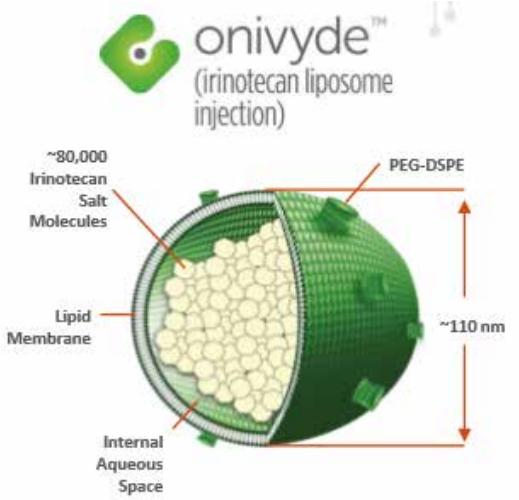
- Rapidly converted to more potent SN-38
- Conjugated and cleared by UGT1A1
- UGT1A1*28 polymorphism at increased risk for neutropenia and diarrhea



https://www.researchgate.net/figure/Irinotecan-Metabolism_fig1_221929791

Liposomal Irinotecan (Onivyde)

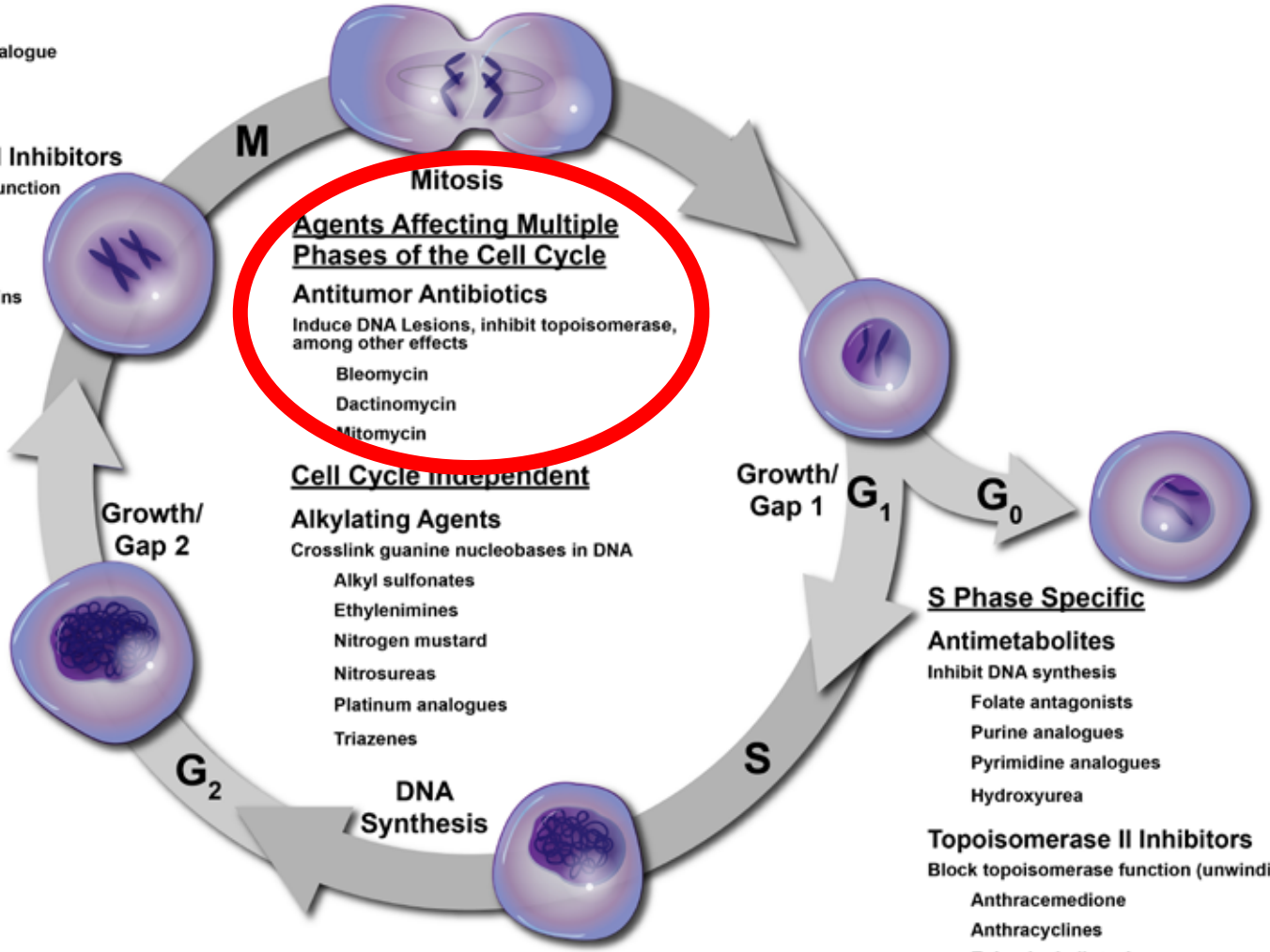
- **Common Uses**: Pancreatic cancer (with 5-FU and leucovorin)
  - Reduce starting dose if homozygous for UGT1A1*28 allele
- **Dosing**: 70 mg/m^2 Q2weeks
- **Toxicities**:
  - Diarrhea (acute and chronic):
    - Atropine for early onset; Loperamide for late onset
  - Fatigue
  - Myelosuppression
- Premedication with corticosteroid and anti-emetics
- NOT interchangeable with traditional irinotecan



https://seekingalpha.com/article/3816696-merrimack-pharmaceuticals-drive-higher-2016-onivyde-pipeline

Topoisomerase II Inhibitors: Etoposide

- **Mechanism** (S/G2 phase):
  - Stabilization of Topo-II-DNA complex causing double stranded DNA breaks
- **Common Uses**: Testicular, SCLC, NHL, BMT
- **Dose Reductions**:
  - CrCl 10-50 ml/min → give 75% of dose
  - TBili 1.5-3 or AST >3x ULN → give 50%
- **Toxicities**:
  - Myelosuppression
  - Alopecia, mucositis, secondary malignancies
  - N/V, especially with PO doses
  - Hypotension (infuse over at least 30-60 min), flushing and headache (30% EtOH in vehicle, can use etoposide phosphate)



M Phase Specific

Antimicrotubule Agents

Inhibit function of microtubules

- Epothilones
- Halichondrin B analogue
- Taxanes
- Vinca alkaloids

Topoisomerase II Inhibitors

Block topoisomerase function (unwinding DNA)

- Anthracemedione
- Anthracyclines
- Epipodophyllotoxins

Agents Affecting Multiple Phases of the Cell Cycle

Antitumor Antibiotics

Induce DNA Lesions, inhibit topoisomerase, among other effects

- Bleomycin
- Dactinomycin
- Mitomycin

Cell Cycle Independent

Alkylating Agents

Crosslink guanine nucleobases in DNA

- Alkyl sulfonates
- Ethylenimines
- Nitrogen mustard
- Nitrosureas
- Platinum analogues
- Triazenes

S Phase Specific

Antimetabolites

Inhibit DNA synthesis

- Folate antagonists
- Purine analogues
- Pyrimidine analogues
- Hydroxyurea

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Block topoisomerase function (unwinding DNA)

- Anthracemedione
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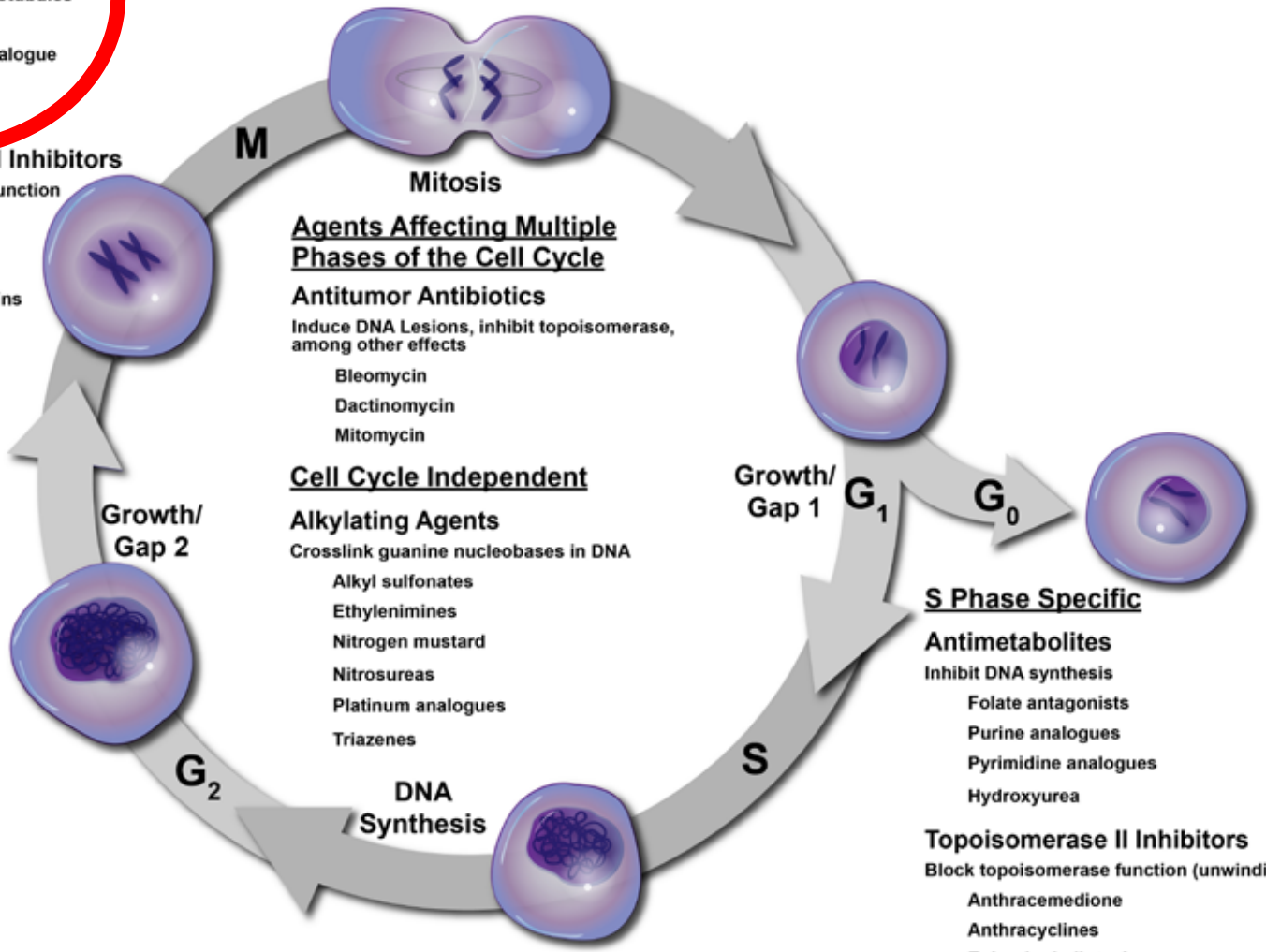
- Epipodophyllotoxins

Antitumor Antibiotics: Bleomycin

- **Mechanism** (G2 phase):
  - Single and double stranded DNA breaks, inhibiting DNA synthesis
- **Common Uses**:
  - Testicular, Hodgkin lymphoma, NHL, squamous cell carcinoma
- **Dosing**:
  - 10-20 units/m^2 or 30 units flat dose
  - **Dose reduction for renal insufficiency** (<50 ml/min)
- **Toxicities**:
  - Hyperpigmentation, rash, fever
  - Pulmonary fibrosis (get baseline PFTs)
    - Increased risk with cumulative dose >400 units and age >70y
  - NOT myelosuppressive



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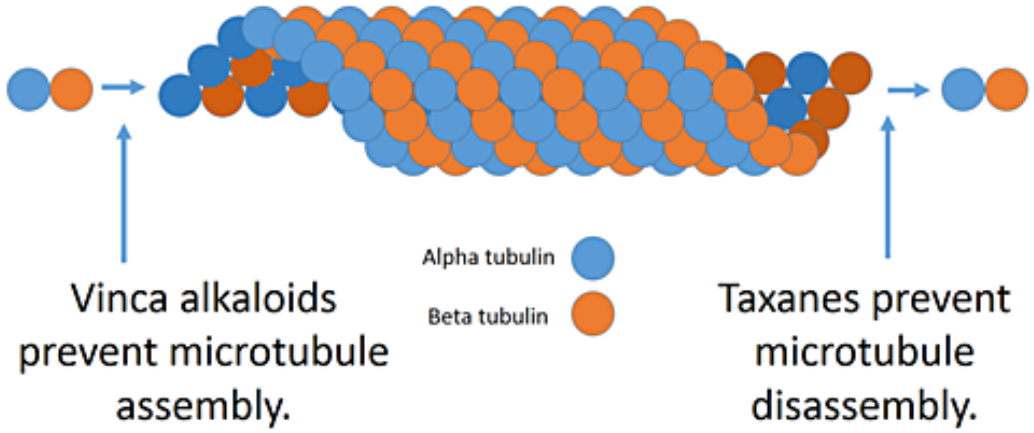
Anti-Microtubular Agents (M phase)

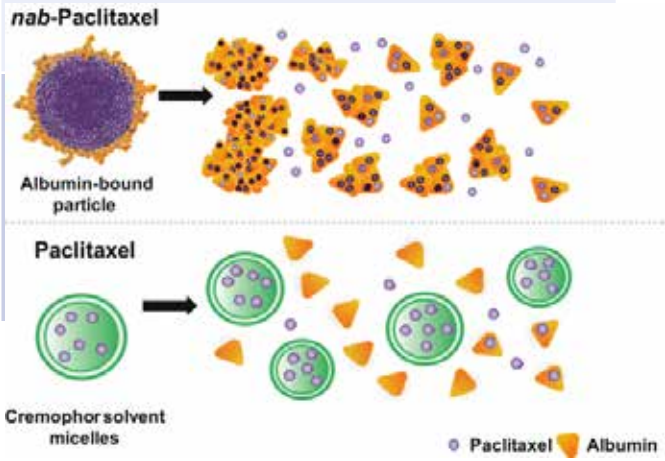


Microtubule Destabilizers	Microtubule Stabilizers
Vinca alkaloids (vincristine/liposomal vincristine, vinblastine, vinorelbine) Eribulin	Taxanes (paclitaxel/nab-paclitaxel, docetaxel, cabazitaxel) Ixabepilone

https://askhematologist.com/principles-of-chemotherapy

Paclitaxel/nab-Paclitaxel

	Paclitaxel (Taxol)	nab-Paclitaxel (Abraxane)
Uses	Multiple solid tumors	
Administration	IV; varying rates for paclitaxel (usually 1, 3, or 24 hours) Abraxane shorter 30 min infusion	
Dosing	80 – 200 mg/m^2, variable schedules	100 – 260 mg/m^2, variable schedules
Common Toxicities	Myelosuppression (↑ w/longer infusion time), Neuropathy (Abraxane > Paclitaxel, ↑ w/ shorter infusion time), mucositis, alopecia, arthralgias/myalgias	
	Hypersensitivity, to diluent	
Premedications	Diphenhydramine 25 mg IV, Ranitidine 50 mg IV , Dexamethasone 20 mg IV or 20 mg PO 12 and 6 hrs prior	



https://link.springer.com/chapter/10.1007/978-981-10-2116-9_6

Docetaxel and Cabazitaxel

	Docetaxel (Taxotere)	Cabazitaxel (Jevtana)
Uses	Prostate, NSCLC, Breast, Ovarian	Prostate
Administration	IV over one hour	
Dosing	60-100mg/m^2 Q21 days	20-25 mg/m^2 Q21 days
Common Toxicities	Myelosuppression (can be severe), neuropathy, alopecia, rash, nausea/vomiting, fatigue	
	Edema, nail changes, mucositis	Diarrhea (can be severe) Hypersensitivity
Premedications	Dexamethasone 8 mg po BID day before, of, after chemo	Diphenhydramine 25 mg IV, Ranitidine 50 mg IV , Dexamethasone 8 mg IV
Notes/Dose Adjustment	Reduce dose for ANY Tbili > ULN, or AST/ALT/Alk Phos elevations	
		Poor affinity for MDR proteins

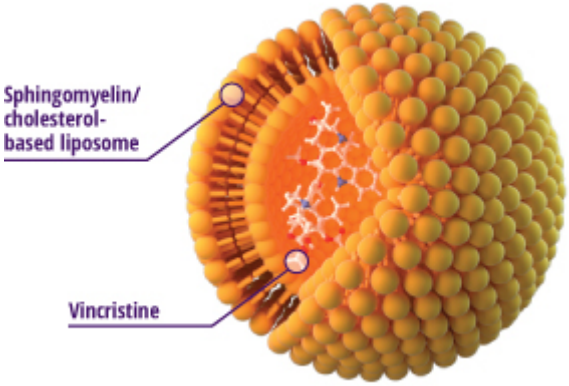
Vinca Alkaloids

- **Common Uses**:
  - Vincristine – leukemias, lymphomas, sarcomas, myeloma
  - Vinblastine – bladder, lymphomas, testicular
  - Vinorelbine – breast, lung

- **Pharmacokinetics**:
  - No CNS penetration
  - All hepatically metabolized (CYP450 3A4) and eliminated via biliary excretion

- **Reduce dose for hepatic insufficiency**

Unique Vinca Toxicities



- **Fatal if given intrathecally**
- Vesicant: Treat with heat, hyaluronidase
- VinCristine
  - **C**NS → peripheral neuropathy, autonomic neuropathy (constipation, paralytic ileus), dose cap at 2 mg
- VinBlastine
  - **B**one marrow suppression
- Vinorelbine:
  - Myelosuppression and CNS, but less severe
- Liposomal vincristine (Marqibo): NOT interchangeable
  - Increased half life vs. vincristine
  - Indicated for ALL, 2.25 mg/m^2 weekly. **No dose cap**
  - Challenging to make, requires specialized equipment

http://www.marqibo.com/hcp/treating.php

Eribulin

- **Origin**: Isolated from marine sponge
- **Common Uses**: Metastatic breast cancer, liposarcoma
- **Dose**: 1.4 mg/m^2 Days 1 and 8 Q21 days
  - **Adjustments for hepatic impairment**
- **Toxicities**:
  - Myelosuppression (neutropenia, anemia)
  - Asthenia/Fatigue
  - Alopecia
  - Peripheral neuropathy
  - QT prolongation

SELECT TARGETED AGENTS

Immunomodulatory Drugs (IMiDs)

- **MOA**: Not fully understood
  - Antiangiogenic
  - Immunomodulating
  - Antineoplastic
  - Inhibits inflammatory cytokine secretion
    - Inhibits TNFα secretion
    - Increase LF-2 and INFγ secretion

- **Black Box Warnings**
  - Teratogenicity (**REMS program required**)
  - Thromboembolism
  - Neutropenia/thrombocytopenia (lenalidomide only)

IMiDs

	Thalidomide (Thalomid)	Lenalidomide (Revlimid)	Pomalidomide (Pomalyst)
Use	MM	MM (maint.), MDS (del 5q)	MM
Dose Adjustments	None	Myelosuppression Renal/Dialysis	Myelosuppression
Common ADEs	Myelosuppression (L, P >> T), neuropathy, bowel changes, fatigue, weakness, edema, nausea, hypotension, rash		
	Sedation, bradycardia	AFib, bradycardia	AFib, dyspnea, hypercalcemia
Serious/Rare ADEs	Hypersensitivity/SJS/TEN/angioedema Secondary malignancies		
	Neuropathy (motor & sensory, may be irreversible); Seizures	Thrombocytopenia, neutropenia (80% Grade 3-4); TLS	CNS effects (dizziness, confusion)
Other		PgP substrate	Major substrate of CYP1A2, 3A4

Proteasome Inhibitors

- **MOA**:
  - 26S proteasome degrades ubiquitinated proteins within the cell thereby regulating intracellular protein concentrations and maintaining homeostasis
  - Inhibition prevents degradation → disrupts homeostasis and normal cell signaling which leads to cell death
- Bortezomib and ixazomib are reversible inhibitors
- Carfilzomib exhibits irreversible binding

Proteasome Inhibitors

	Bortezomib (Velcade)	Carfilzomib (Kyprolis)	Ixazomib (Ninlaro)
Use	MM, Mantle Cell Lymphoma	MM Combo with len/dex after 1-3 lines; Monotherapy after 1 line of therapy	MM Combo with len/dex after 1 line of therapy
Administration	SQ, IV	IV	PO
Dosing	1.3 mg/m^2 days 1, 4, 8 and 11 Q21 days 1.5 mg/m^2 days 1, 8, 15, and 22 Q28 days	Cycle 1 20 mg/m^2 days 1, 2 27 mg/m^2 days 8, 9,15,16 Q28 days Can increase up to 56 mg/m^2	4 mg Days 1, 8, and 15 Q28 days on an empty stomach
PK/PD	Not influenced by renal dysfunction, give after dialysis		Give 3 mg for CrCl < 30 ml/min Not dialyzable

Proteasome Inhibitors

	Bortezomib (Velcade)	Carfilzomib (Kyprolis)	Ixazomib (Ninlaro)
ADEs	Fatigue, malaise, N/V, diarrhea, constipation, neutropenia, **thrombocytopenia**, **peripheral neuropathy** Cardiotoxicity: orthostatic hypotension, edema, CHF		
Comparison	**Most peripheral neuropathy**: IV > SubQ	**Most cardiotoxic** Rare: pulmonary toxicity, RPLS, TLS, acute liver	Less peripheral neuropathy
Drug Interactions	CYP3A4, CYP2C19	PgP	CYP3A4; PgP
Pre-medications		Dexamethasone 4mg PO/IV	
Notes		Cap BSA at 2.2 m^2 Give fluids prior to first cycle, then PRN	

Daratumumab (Darzalex/Darzalex Faspro)

- **MOA**:
  - IgG1κ human mAB directed against CD38
  - Inhibits growth by inducing apoptosis directly through Fc mediated cross linking & immune-mediated tumor cell lysis
- **Dosing**: 16 mg/kg IV or 1800 mg SubQ
  - Weeks 1-8: once weekly
  - Weeks 9-24: Q2 weeks
  - Weeks 25+: Q4 weeks
- **Test Interference**:
  - May be detected on SPEP and immunofixation assays
  - Via binding to CD38 on RBCs, may result in a positive Coombs test
  - Daratumumab masks antibody detection to minor antigens in the serum
    - **Type and screen patients prior to therapy**

Isatuximab-irfc (Sarclisa)

- **MOA**:
  - IgG1-derived chimeric mAB directed against CD38
- **Dosing**:
  - C1: 10 mg/kg days 1, 8, 15, 22 of a 28 day cycle
  - C2+: 10 mg/kg on days 1 and 15 of a 28 day cycle
  - Given with pomalidomide
- **Test Interference**:
  - Same as daratumumab

Elotuzumab (Empliciti)

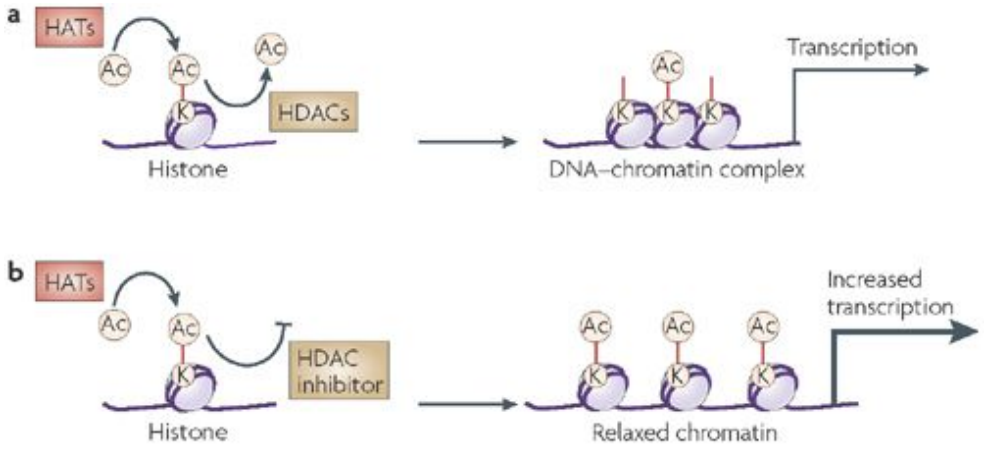
- **MOA**:
  - Antibody directed against signaling lymphocytic activation molecule family member 7 (SLAMF7), expressed on most myeloma and natural killer cells
  - Directly activates natural killer cells through SLAMF7 pathway and Fc receptors
- **Dosing**:
  - Cycles 1-2: 10 mg/kg Days 1, 8, 15, and 22 Q28 days
  - Cycle 3+: 10 mg/kg Days 1, 15 Q28 days (lenalidomide/dex combo)
  - Cycle 3+: 20 mg/kg Days 1 Q28 days (pomolidomide/dex combo)
- **Test Interference**:
  - May be detected on SPEP and immunofixation assays

Selinexor (Xopovio)

- **MOA**:
  - Reversibly inhibits nuclear export of tumor suppressor proteins, growth regulators, and mRNAs of oncogenic proteins via blockage of exportin 1
- **Dosing**:
  - 80 mg PO twice weekly
- **ADEs**:
  - Bone marrow suppression
  - GI: Nausea, diarrhea, vomiting
  - Fatigue

HDAC Inhibitor Class Overview

- Histone deacetylases catalyze the removal of acetyl groups from the lysine residues of proteins
  - Allows for accumulation of acetylated histones → changes in chromatin structure and activation of transcription factors → cell cycle arrest and/or apoptosis
- T cell lymphomas (CTCL, PTCL), myeloma
- PO and IV options
  - PO: Vorinostat, Panobinostat
  - IV: Romidepsin, Belinostat



Nature Reviews | Drug Discovery

FLT3 Inhibitors

	Midostaurin (Rydapt)	Gilteritinib (Xospata)
Use	AML, FLT-3 mutated Mast cell leukemia Systemic mastocytosis	AML, FLT-3 mutated
Dose	AML: 50 mg PO BID days 8-21 Other: 100 mg PO BID	120mg PO daily
Common Toxicities	Nausea, diarrhea, hyperglycemia, electrolyte abnormalities, increased LFTs, increased SCr, QT prolongation	
	Neutropenia, leukopenia, anemia, thrombocytopenia	Constipation, hypertriglyceridemia,
Rare/Serious Toxicities		Differentiation syndrome
Drug Interactions	CYP3A4 inducers and inhibitors	

IDH Inhibitors

	Enasidenib (Idhifa)	Ivosidenib (Tibsovo)
Use	Relapsed/refractory AML, IDH2 mutated	Relapsed/refractory AML, IDH1 mutated
Dose	100 mg PO daily	500 mg PO daily
Common Toxicities	Differentiation syndrome (treat with steroids) Electrolyte imbalances (hypocalcemia, hypokalemia)	
	Nausea, vomiting, diarrhea, anorexia Elevated bilirubin	QTc prolongation, LFT elevations
Notes		ECG monitoring weekly for first month

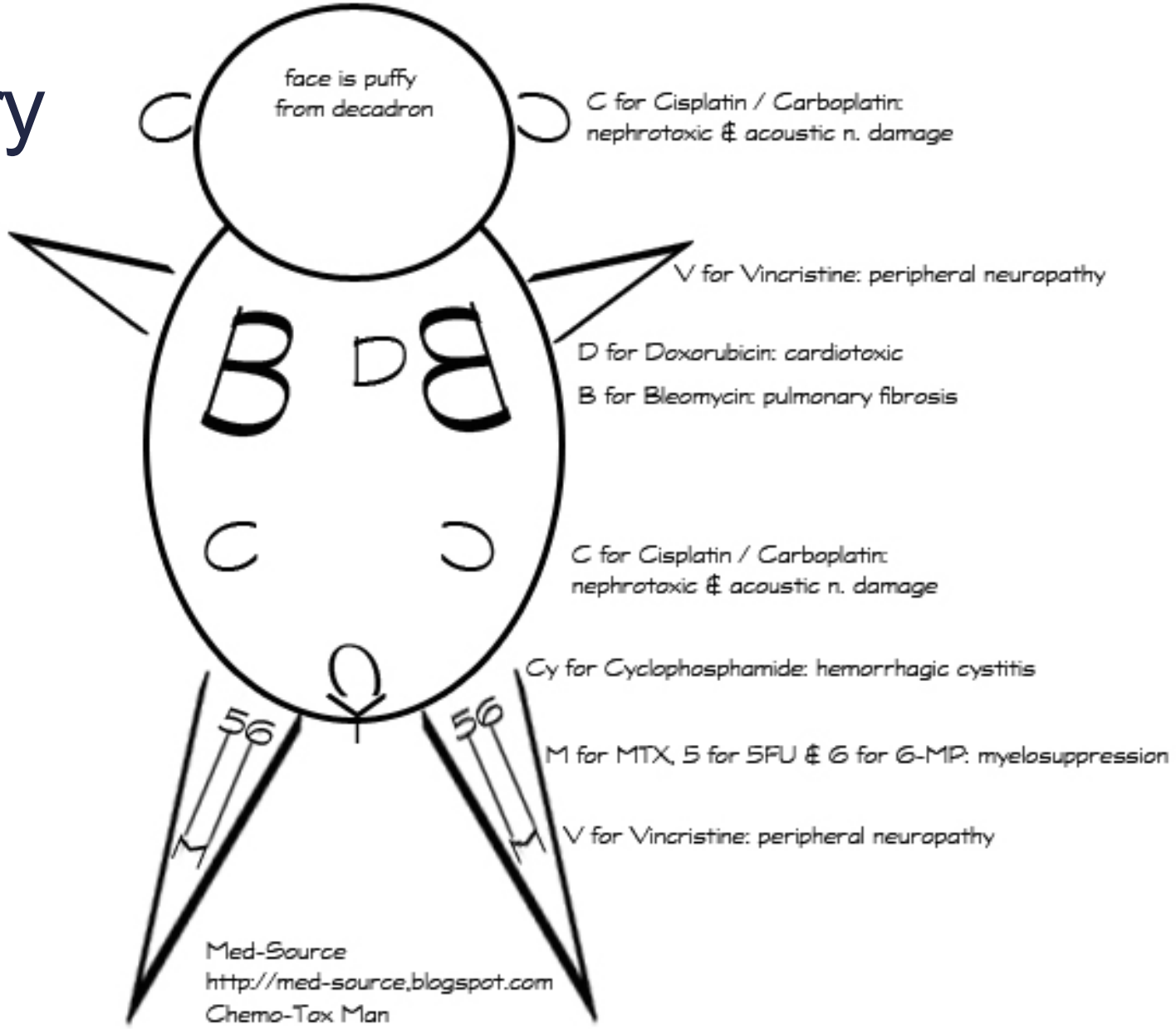
Non-Malignant Heme Drugs

- **Caplicizumab-yhdp (Cablivi)**
  - **Indication**: Thrombotic thrombocytopenic purpura, acquired (aTTP)
  - **Dose**: 11mg IV once before plasma exchange (first dose) and 11mg SubQ daily post plasma exchange (all subsequent doses)
  - **MOA**: Von Willebrand factor (vWF) – directed mAB that targets the A1-domain of vWF reducing platelet adhesion and consumption
- **Luspatercept-aamt (Reblozyl)**
  - **Indication**: Anemia due to beta thalassemia, MDS
  - **Dose**: 1 mg/kg SubQ Q3weeks
    - Max dose 1.25 mg/kg for beta thalassemia; 1.75 mg/kg for MDS
  - **MOA**: Recombinant fusion that inhibits endogenous TGF-beta superfamily, increasing differentiation/proliferation of erythroid precursors
- **Crizanlizumab-tmca (Adakveo)**
  - Indication: Sickle cell disease
  - Dose: 5 mg/kg IV Q2weeks for 2 doses, then Q4weeks
  - MOA: Antibody that binds to P-selectin, preventing adhesion of sickle erythrocytes to vessels, decreasing frequency of pain crisis

Non-Malignant Heme Drugs

- **Givosiran (Givlaari)**
  - **Indication**: Acute hepatic porphyria
  - **Dose**: 2.5 mg/kg SubQ monthly
  - **MOA**: Causes degredation of aminolevulinate synthase 1 (ALAS1) mRNA in hepatocytes, leading to reduced circulating levels of neurotoxic intermediates that lead to disease manifestations
- **Afamelanotide (Scenesse)**
  - **Indication**: Erythropoietic protoporphyria
  - **Dose**: 16 mg SubQ implant Q2months
  - **MOA**: Melanocortin receptor agonist that binds to MC1-R, increasing production of eumelanin in the skin

Summary


face is puffy
from decadron
C for Cisplatin / Carboplatin:
nephrotoxic & acoustic n. damage
V for Vincristine: peripheral neuropathy
D for Doxorubicin: cardiotoxic
B for Bleomycin: pulmonary fibrosis
C for Cisplatin / Carboplatin:
nephrotoxic & acoustic n. damage
Cy for Cyclophosphamide: hemorrhagic cystitis
M for MTX, 5 for 5FU & 6 for 6-MP: myelosuppression
V for Vincristine: peripheral neuropathy
Med-Source
http://med-source.blogspot.com
Chemo-Tox Man

Thank you!

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CANCER PHARMACOLOGY I

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Lead Clinical Pharmacist, Stem Cell Transplant/Immunotherapy

University of Washington Medical Center & Seattle Cancer Care Alliance

August 13, 2020

APPENDICES

Selected Drugs Requiring Dose Reduction or Avoidance for Renal Dysfunction

- Cisplatin
- Carboplatin* (Calvert equation accounts for renal function)
- Methotrexate
- Capecitabine
- Etoposide
- Fludarabine
- Arsenic trioxide
- Azacitidine
- Cytarabine (high dose)
- Bleomycin
- 6-mercaptopurine
- 6-thioguanine
- Oxaliplatin
- Ifosfamide
- Topotecan
- Pemetrexed

The Oncologist 2007;12:1070 –1083

Selected Drugs Requiring Dose Reduction for Hepatic Dysfunction

- Doxorubicin
- Liposomal doxorubicin
- Irinotecan
- Etoposide
- Eribulin
- Docetaxel
- Cabazitaxel
- Ixabepilone
- Vinca alkaloids
- Methotrexate
- 5-FU
- 6-mercaptopurine
- 6-thioguanine
- Paclitaxel
- Gemcitabine

The Oncologist 2007;12:1070 –1083

Abbreviations

- BBB- Blood Brain Barrier
- DL_{CO}- Diffusing capacity for carbon monoxide
- DTIC- Dacarbazine
- FRB- FKB12-rapamycin binding
- FVC- Forced Vital Capacity
- GBM- Glioblastoma Multiforme
- LFT- Liver Function Test
- LVEF- Left Ventricular Ejection Fraction
- MOA- Mechanism of Action
- PCP/PJP- Pneumocystis carinii/jiroveci Pneumonia
- SIADH- Syndrome of Inappropriate Antidiuretic Hormone
- XRT- Radiation Therapy