

# CANCER PHARMACOLOGY I

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Alliance

# 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

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## M Phase Specific

### Antimicrotubule Agents

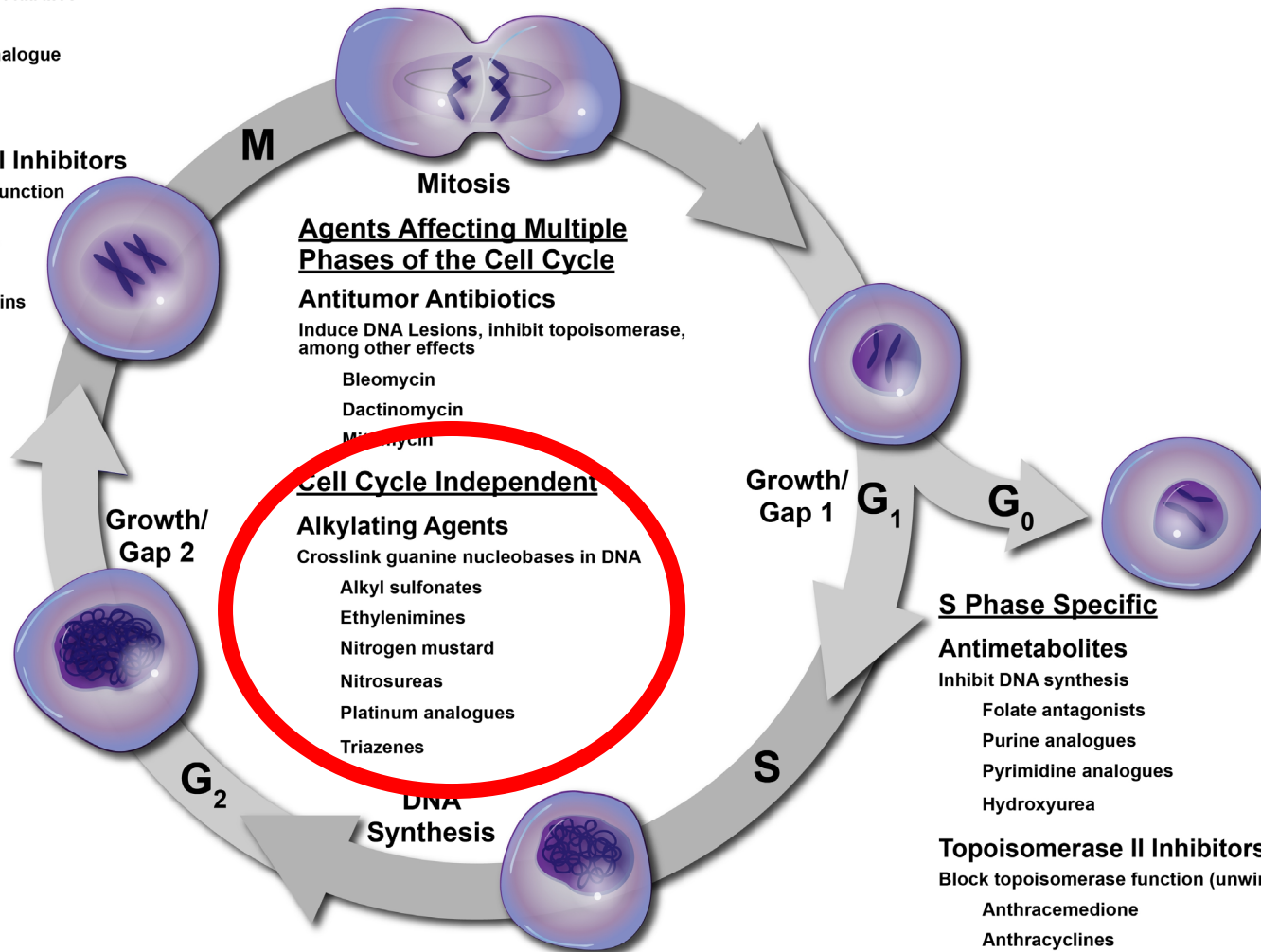
Inhibit function of microtubules

- Epothilones
- Halichondrin B analogue
- Taxanes
- Vinca alkaloids

### Topoisomerase II Inhibitors

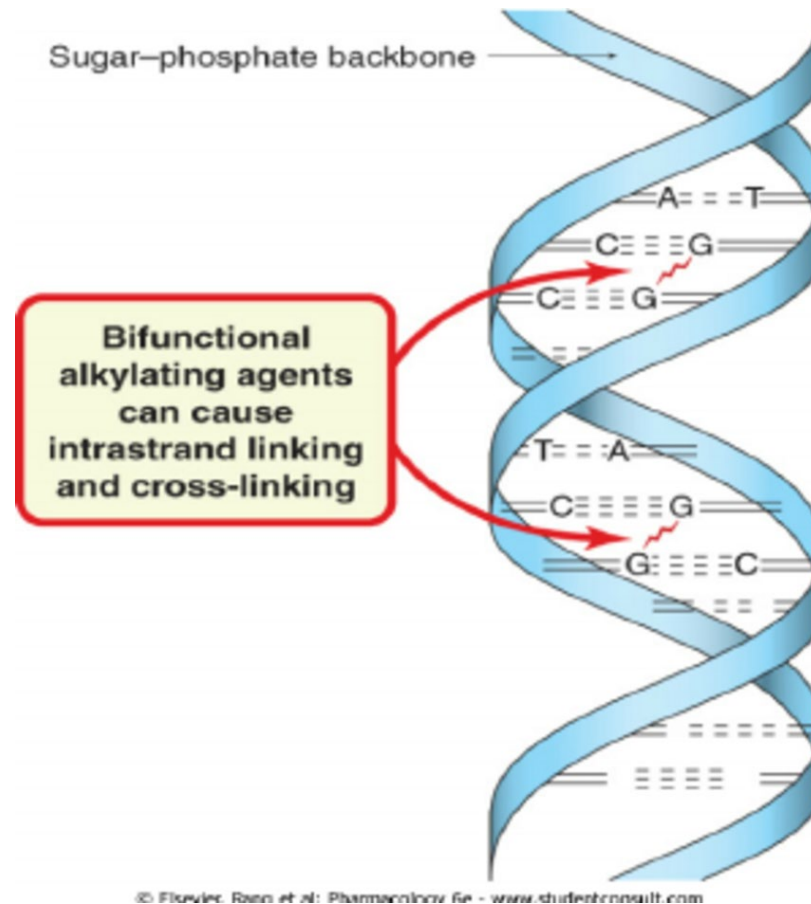
Block topoisomerase function (unwinding DNA)

- Anthracemedione
- Anthracyclines
- Epipodophyllotoxins



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

# Alkylating Agents



# Alkylating Agents: Class Toxicities

- Infertility: Oligospermia, amenorrhea
- Teratogenic: exposure in 1<sup>st</sup> trimester associated with increased risk of fetal malformations
  - Therapy in 2<sup>nd</sup> or 3<sup>rd</sup> 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
<b>Common uses</b>	Breast, lymphoma, leukemia, sarcoma, HSCT, immunosuppressive tx	Sarcoma, lymphoma, testicular
<b>Dosing</b>	PO: 500-300mg/m <sup>2</sup> IV: 250-2000mg/m <sup>2</sup> ; 60-100mg/kg	IV: 1-5g/m <sup>2</sup> /d
<b>Common Toxicities</b>	Myelosuppression (platelet sparing) Delayed nausea/vomiting (dose-related) Alopecia	
<b>Rare/ Serious Toxicities</b>	<b>Hemorrhagic cystitis</b>	
	<b>Cardiotoxicity</b> w/ high dose Interstitial pneumonitis SIADH	Fanconi's syndrome <b>Encephalopathy</b> (treat with methylene blue)
<b>Notes</b>	Drug-drug interaction with warfarin – monitor PT/INR <b>Dose reduce for renal dysfunction</b>	
	Uroprotection with mesna (Doses >1500-2000mg/m <sup>2</sup> )	Uroprotection with mesna <b>ALWAYS</b> (60% of total ifos dose given pre and post infusion)



# Nitrogen Mustard

	Melphalan (Alkeran; Evomela)	Melphalan Flufenamide (Pepaxto)
<b>Common uses</b>	HSCT, multiple myeloma, ovarian	Multiple myeloma (R/R)
<b>Dosing</b>	PO: 0.15-0.25 mg/kg; 4-9 mg/m <sup>2</sup> IV: 60-200 mg/m <sup>2</sup>	IV: 40mg Q28days
<b>Dose Reductions</b>	Variable	1: 30mg 2: 20mg
<b>Common Toxicities</b>	Diarrhea, nausea, vomiting Anemia, neutropenia, thrombocytopenia Alopecia	
<b>Notes</b>	Dose reduce for renal dysfunction Only comes orally as 2 mg tablets Cryotherapy for HSCT doses <u>Stability</u> : Alkeran 1 hr Evomela 4 hrs	No dose adjustments for renal function Not indicated for HSCT <u>Stability</u> : 1 hr room temp 6 hrs refrigerated

# 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)



# 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

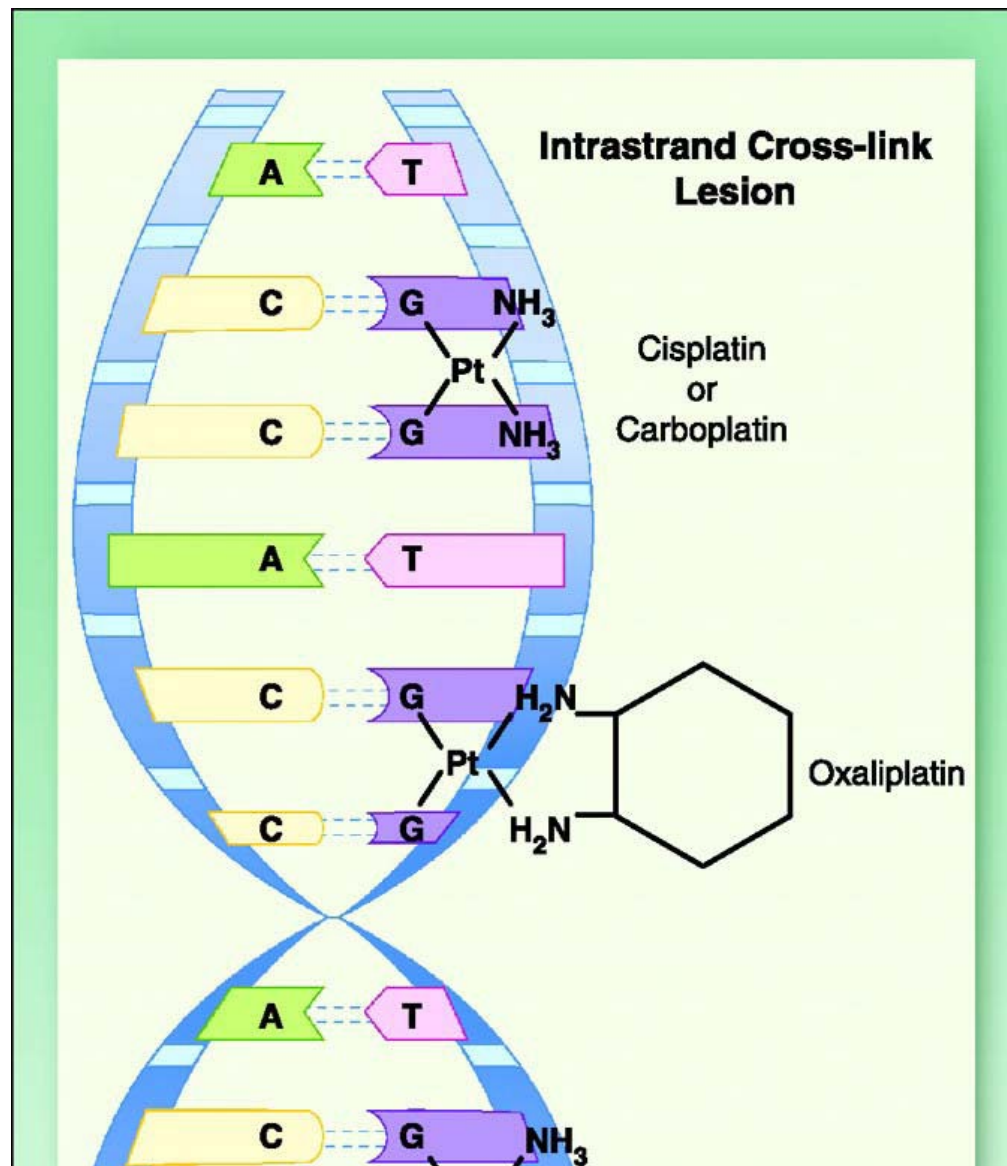
- **Common Uses:** Lymphomas, brain tumors, pheochromocytoma (dacarbazine)
- **Major Toxicities:** Highly emetogenic, bone marrow suppression
- Procarbazine: a monoamine oxidase inhibitor (MAOI)
  - Potentiates other CNS drugs (barbiturates, opiates, antihistamines)
  - Hypertensive reactions w/ other 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 sx's
  - Photosensitivity



# Platinum Agents



# Platinum Agents: Dosing

	Cisplatin	Carboplatin	Oxaliplatin
<b>Common Uses</b>	Broad spectrum activity against numerous malignancies		
<b>Dosing</b>	Up to 100 mg/m <sup>2</sup> Q21 days (50-75 mg/m <sup>2</sup> 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 <sup>2</sup> Q2-3 weeks
<b>Notes</b>	Excreted in urine <b>50% dose reduction for CrCl &lt;60 ml/min</b> (or split dosing)	Can give in HD	Rapid and extensive nonenzymatic metabolism

# Platinum Agents: Variations in Toxicity

Cisplatin	Carboplatin	Oxaliplatin
<ul style="list-style-type: none"> <li>• <b>Severe N/V</b>, acute, delayed</li> <li>• <b>Renal dysfunction</b></li> <li>• Electrolyte wasting</li> <li>• Peripheral Neuropathy</li> <li>• Reduces clearance of other drugs (give other drug first)</li> <li>• <b>Ototoxicity/tinnitus</b>, high frequency hearing loss (cumulative, irreversible)</li> <li>• SIADH</li> </ul>	<ul style="list-style-type: none"> <li>• Moderate-severe N/V</li> <li>• Peripheral neuropathy</li> <li>• <b>Myelosuppression</b> (thrombocytopenia)</li> <li>• <b>Hypersensitivity reaction</b> after dose 7-9 (can desensitize)</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Neuropathy</b>, acute &amp; chronic (sensory/peripheral, dose limiting)               <ul style="list-style-type: none"> <li>• <i>Acute</i>: Triggered by cold</li> <li>• Laryngo-pharyngeal dysesthesias with choking sensation</li> </ul> </li> <li>• Dose-dependent neurotoxicity, typically &gt;850mg/m<sup>2</sup> (reversible)</li> </ul>



# 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 <sup>2</sup>	0.14%
500-550 mg/m <sup>2</sup>	4%
550-600 mg/m <sup>2</sup>	18%
> 600 mg/m <sup>2</sup>	36%

# ARS Question 1

You have a patient scheduled to receive cisplatin dosed at 75 mg/m<sup>2</sup> today in the infusion center. Which of the following does NOT need to be included in the supportive care orders?

- A. Hydration with potassium and magnesium
- B. Anti-emetics (including 3 different drug classes)
- C. Methylene blue every 6 hours
- D. Baseline audiology exam review

## ARS Question 2

Your patient is being treated with temozolomide (Temodar) and XRT. What supportive care medication(s) needs to be ordered?

- A. Hydration with calcium and magnesium
- B. Bactrim for PJP prophylaxis
- C. Anti-emetics for highly emetogenic chemotherapy
- D. Antiseizure prophylaxis

# Misc. Cell Cycle Nonspecific Agents

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

# 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/RAR $\alpha$ 
  - 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 1<sup>st</sup> 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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## M Phase Specific

### Antimicrotubule Agents

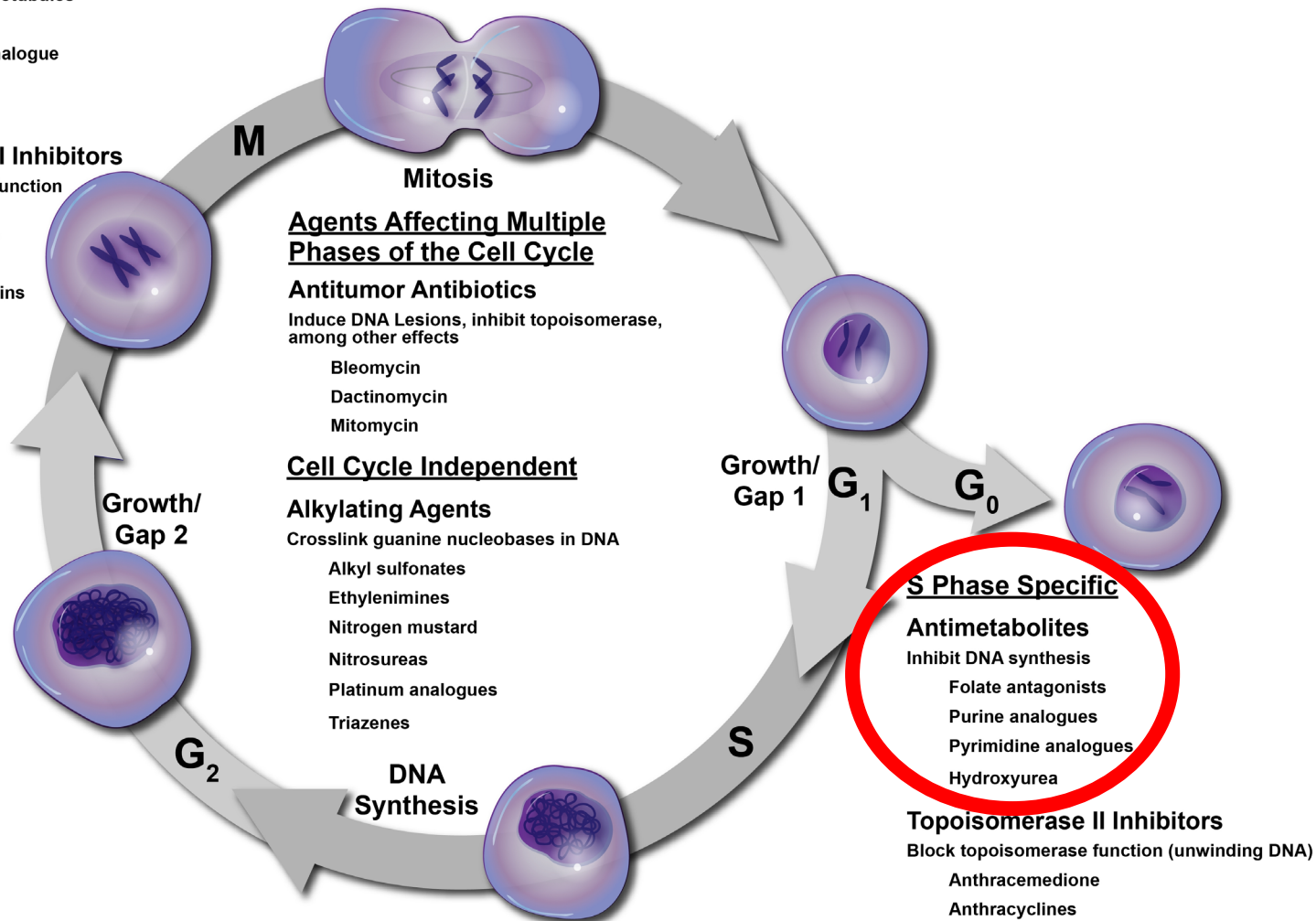
Inhibit function of microtubules

Epothilones  
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Taxanes  
Vinca alkaloids

### Topoisomerase II Inhibitors

Block topoisomerase function  
(unwinding DNA)

Anthrasedione  
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# Antimetabolites: Folate Antagonists

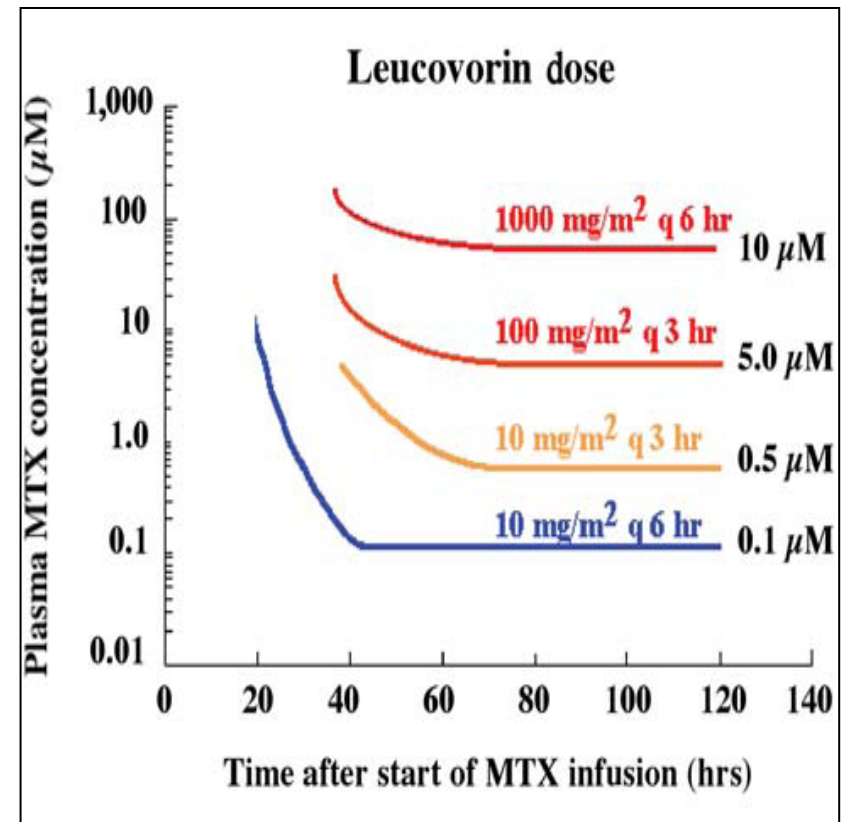
- **Mechanism (S phase):**
  - Actively transported into cell by transport proteins, metabolized to polyglutamated forms to exert cytotoxic effects
  - Inhibits dihydrofolate reductase (DHFR) = Causes depletion of intracellular reduced folate essential for thymidylate and purine synthesis
- **Drugs:** 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 ( $>1\text{g/m}^2$ ) therapeutic concentrations in CSF
- Intrathecal may result in myelosuppression and/or mucositis as detectable serum levels may be achieved

# Methotrexate: High-Dose Therapy

- Doses  $\geq 500$  mg/m<sup>2</sup> 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)

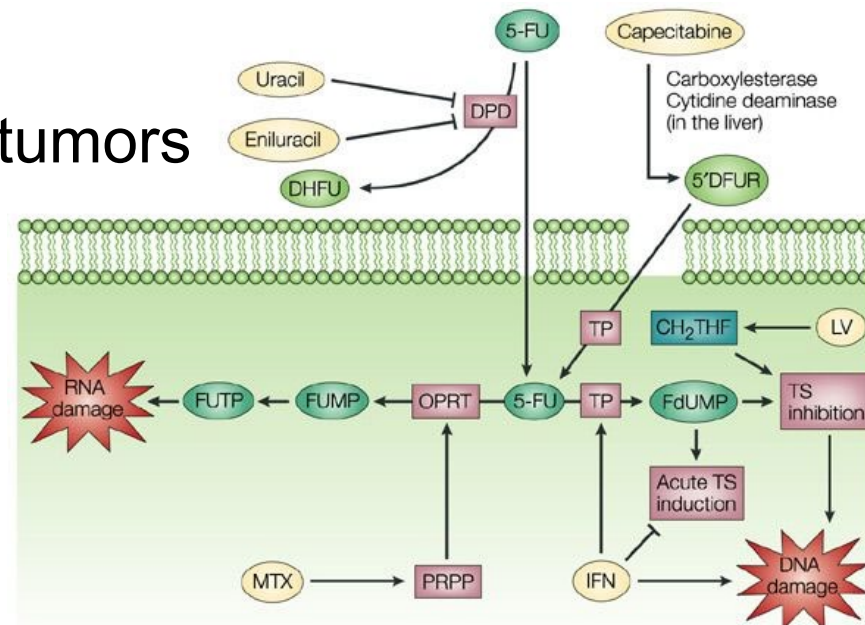
- **Common Uses:** Solid tumors
- **Elimination:** Mainly renal excretion
  - Same drug interactions as methotrexate (avoid NSAIDs)
  - **Dose reduction for renal dysfunction**
    - Not recommended if CrCl <45 mL/min
- **Major Toxicities:**
  - Myelosuppression
  - Generalized pruritic, painful rash
    - 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



# 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

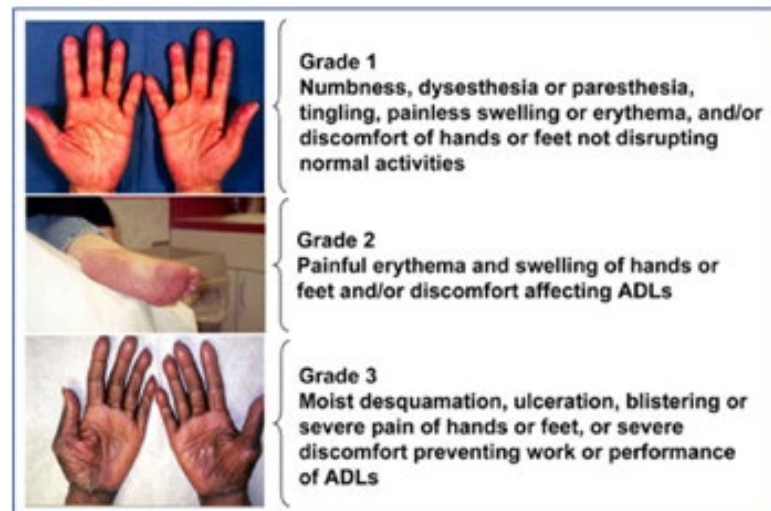
# 5-Fluorouracil: Toxicities

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 Trifluridine 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<sup>2</sup>)

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

## High-Dose bolus (1-3 g/m<sup>2</sup>)

- 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 (HMAs)

- **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

# Oral HMAs

	Azacitidine (Onureg)	Decitabine/Cedazuridine (Inqovi)
<b>Use</b>	AML (maintenance)	MDS
<b>Dose</b>	300mg PO days 1-14 Q28Days	35mg/100mg days 1-5 Q28Days
<b>Dose Reductions</b>	1: 200 mg days 1-14 2: 200 mg days 1-7	1: Days 1-4 2: Days 1-3 3: Days 1, 3, 5
<b>Common Toxicities</b>	Neutropenia, anemia, thrombocytopenia	
	Nausea, vomiting, diarrhea	Constipation, increased LFTs, fatigue
<b>Notes</b>	Administer first 2 cycles with antiemetic 30 min prior	Minimum of 4 cycles Take on an empty stomach

# Antimetabolites: Purine Analogs

Class	Chemotherapy Agent
<b>Purine Analogs</b>	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

## M Phase Specific

### Antimicrotubule Agents

Inhibit function of microtubules

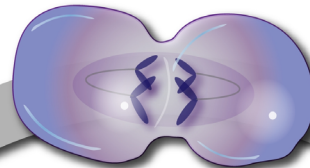
Epothilones  
Halichondrin B analogue  
Taxanes  
Vinca alkaloids

### Topoisomerase II Inhibitors

Block topoisomerase function  
(unwinding DNA)

Anthracedione  
Anthracyclines  
Epipodophyllotoxins

**M**



**Mitosis**

## Agents Affecting Multiple Phases of the Cell Cycle

### Antitumor Antibiotics

Induce DNA Lesions, inhibit topoisomerase, among other effects

Bleomycin  
Dactinomycin  
Mitomycin

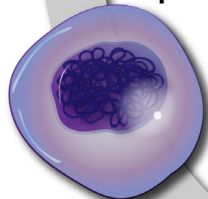
## Cell Cycle Independent

### Alkylating Agents

Crosslink guanine nucleobases in DNA

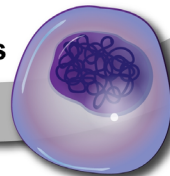
Alkyl sulfonates  
Ethylenimines  
Nitrogen mustard  
Nitrosureas  
Platinum analogues  
Triazenes

**Growth/  
Gap 2**

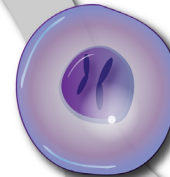


**G<sub>2</sub>**

**DNA  
Synthesis**

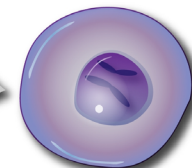


**Growth/  
Gap 1**



**G<sub>1</sub>**

**G<sub>0</sub>**



## S Phase Specific

### Antimetabolites

Inhibit DNA synthesis

Folate antagonists  
Purine analogues  
Pyrimidine analogues  
Hydroxyurea

### Topoisomerase II Inhibitors

Block topoisomerase function (unwinding DNA)

Anthracedione  
Anthracyclines  
Epipodophyllotoxins

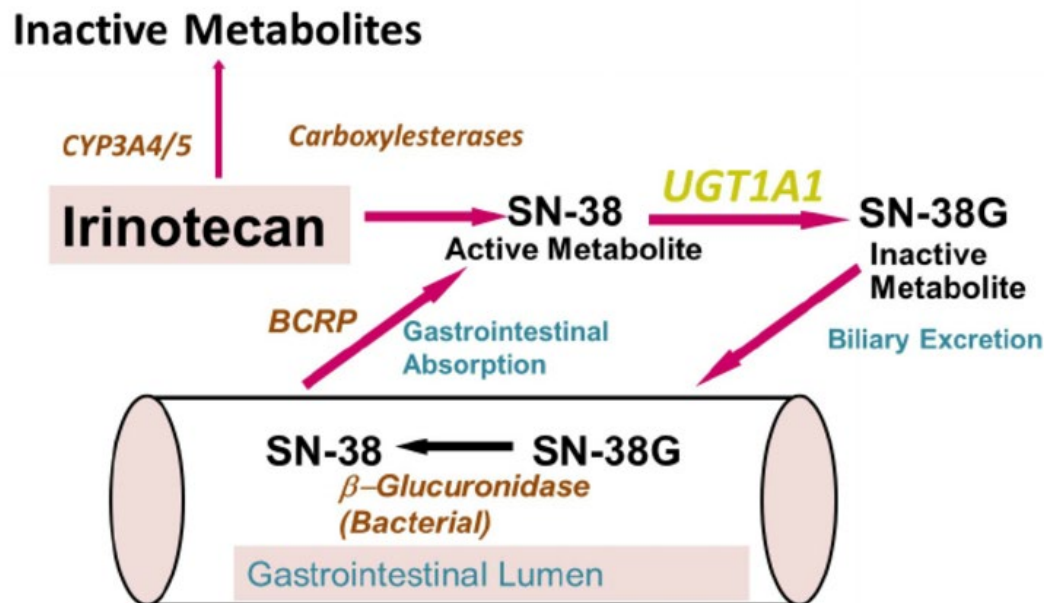
# Topoisomerase I Inhibitors

- **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**



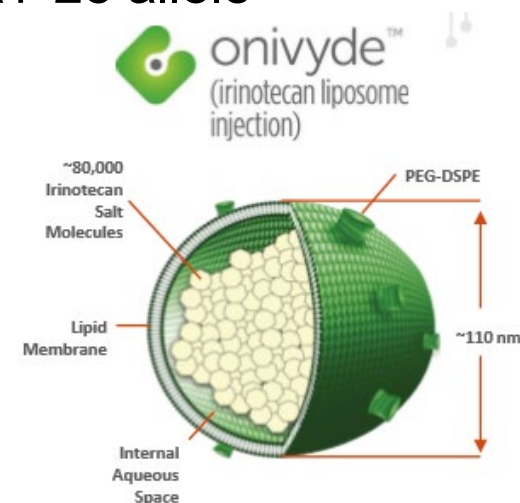
# Irinotecan and SN-38

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



# 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<sup>2</sup> 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



# 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)

## ARS Question 3

Your patient on capecitabine for the past 2 months calls in to the clinic reporting increased pain in the palms and soles to the point where they are having trouble standing up at work and had to call in sick the past 3 days. What is the best course of action?

- A. Continue capecitabine at the same dose and suggest a better fitting pair of shoes
- B. Hold capecitabine and suggest a nice hot bath or trip to the sauna
- C. Continue capecitabine, but decrease the dose 50% for the next cycle
- D. Hold capecitabine until it improves, then decrease the dose 25% for the next cycle

## M Phase Specific

### Antimicrotubule Agents

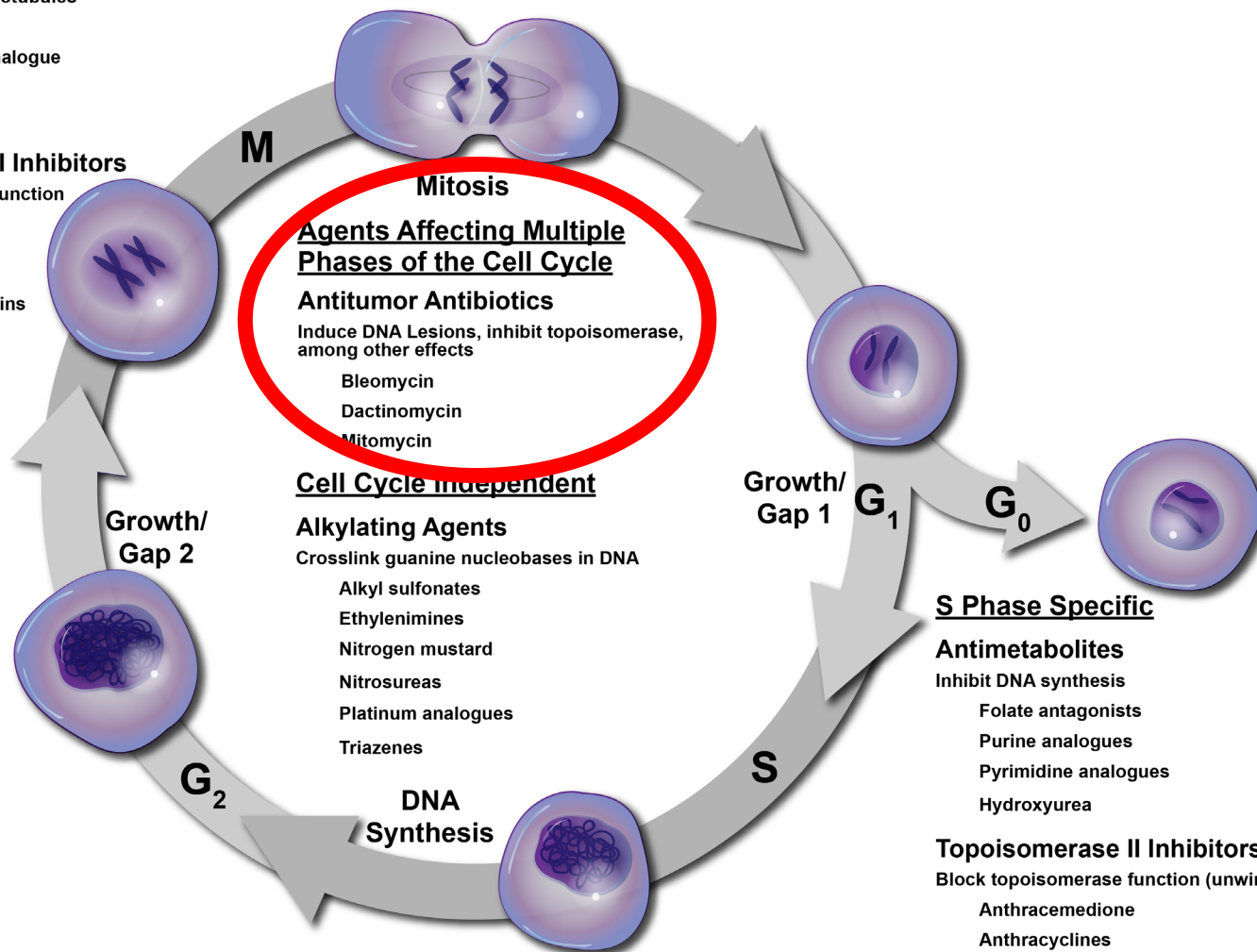
Inhibit function of microtubules

Epothilones  
Halichondrin B analogue  
Taxanes  
Vinca alkaloids

### Topoisomerase II Inhibitors

Block topoisomerase function  
(unwinding DNA)

Anthracedione  
Anthracyclines  
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<sup>2</sup> 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

### M Phase Specific

#### **Antimicrotubule Agents**

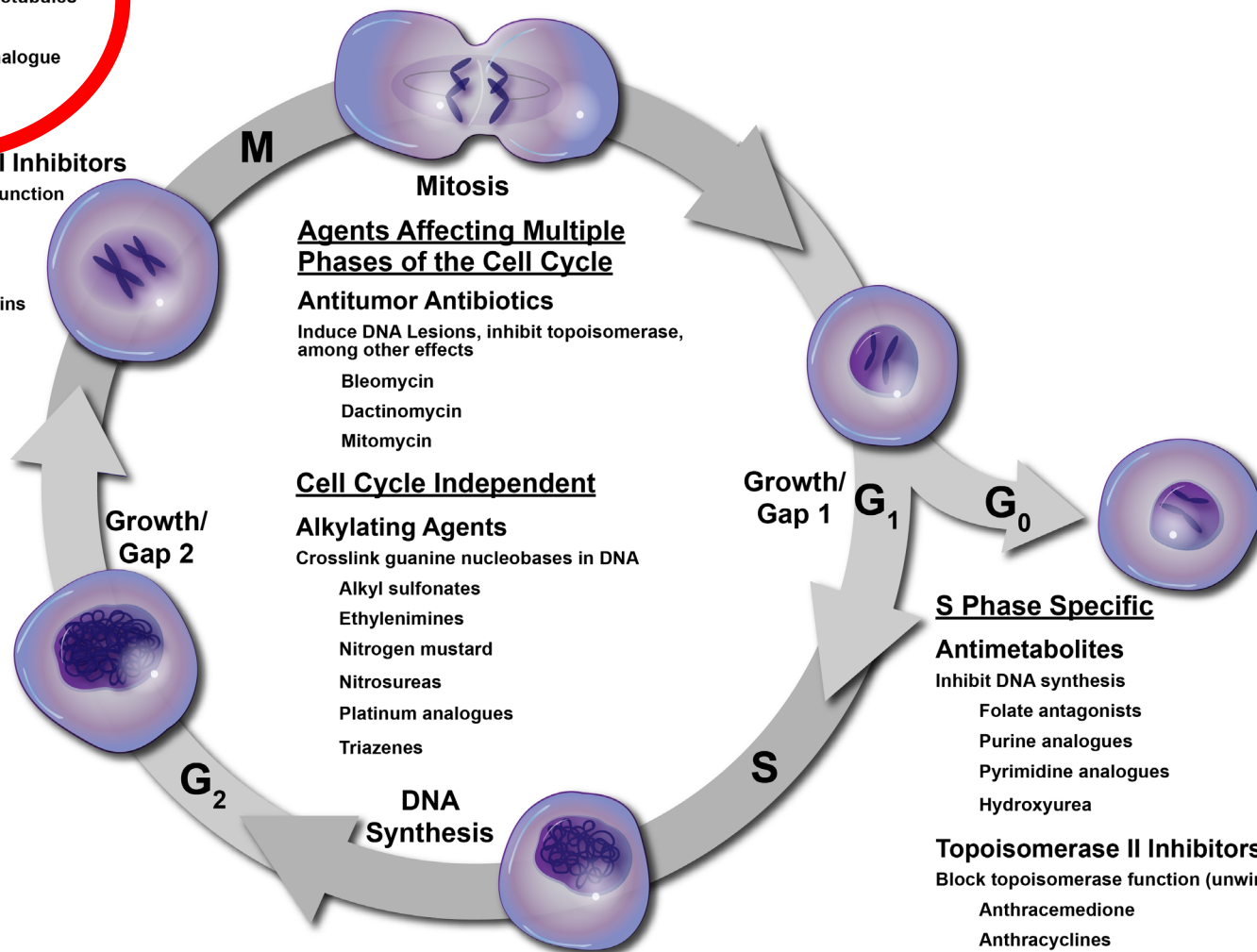
Inhibit function of microtubules

Epothilones  
Halichondrin B analogue  
Taxanes  
Vinca alkaloids

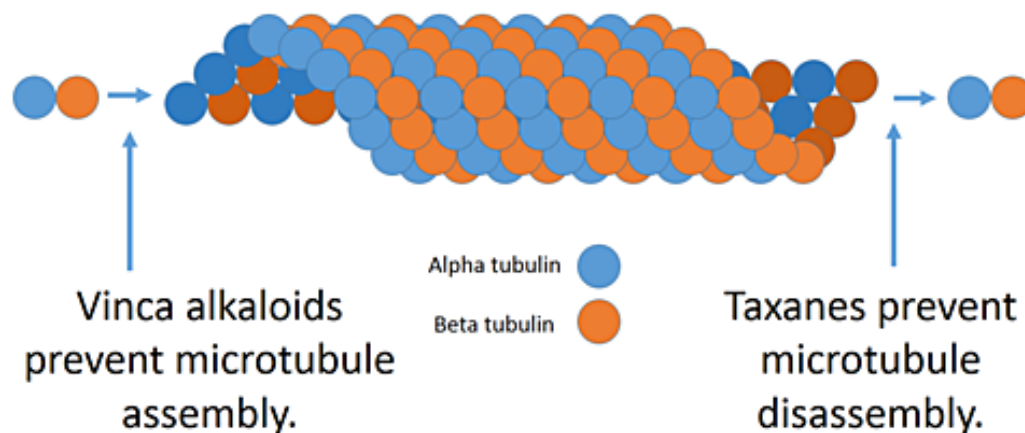
#### **Topoisomerase II Inhibitors**

Block topoisomerase function  
(unwinding DNA)

Anthracedione  
Anthracyclines  
Epipodophyllotoxins



# Anti-Microtubular Agents (M phase)



## Microtubule Destabilizers

Vinca alkaloids  
(vincristine/liposomal  
vincristine, vinblastine,  
vinorelbine)

Eribulin

## Microtubule Stabilizers

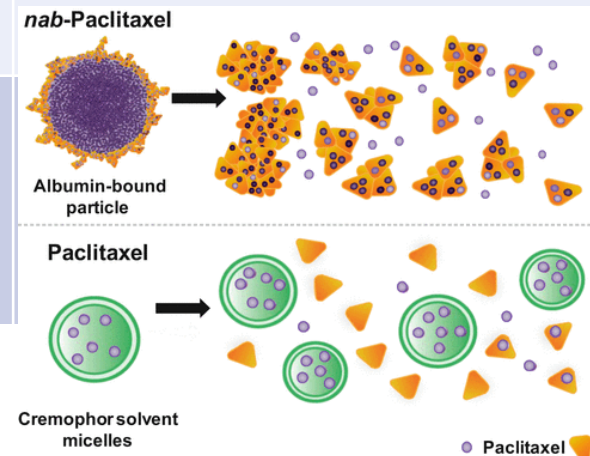
Taxanes  
(paclitaxel/nab-paclitaxel,  
docetaxel, cabazitaxel)

Ixabepilone



# Paclitaxel/nab-Paclitaxel

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



# Docetaxel and Cabazitaxel

	Docetaxel (Taxotere)	Cabazitaxel (Jevtana)
<b>Uses</b>	Prostate, NSCLC, Breast, Ovarian	Prostate
<b>Administration</b>	IV over one hour	
<b>Dosing</b>	60-100mg/m <sup>2</sup> Q21 days	20-25 mg/m <sup>2</sup> Q21 days
<b>Common Toxicities</b>	Myelosuppression (can be severe), neuropathy, alopecia, rash, nausea/vomiting, fatigue	
	Edema, nail changes, mucositis	Diarrhea (can be severe) Hypersensitivity
<b>Premedications</b>	Dexamethasone 8 mg po BID day before, of, after chemo	Diphenhydramine 25 mg IV, Ranitidine 50 mg IV, Dexamethasone 8 mg IV
<b>Notes/Dose Adjustment</b>	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

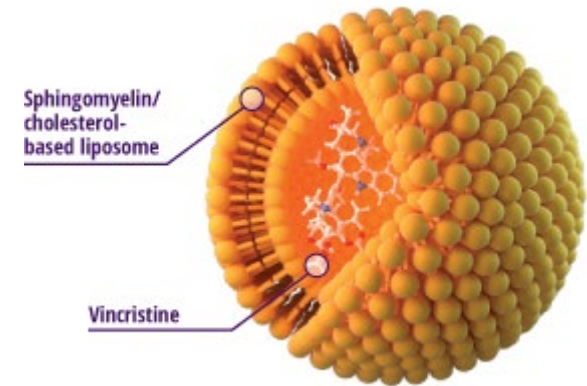
- **Pharmacokinetics:**

- 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
  - CNS → peripheral neuropathy, autonomic neuropathy (constipation, paralytic ileus), dose cap at 2 mg
- VinBlastine
  - Bone 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<sup>2</sup> weekly. **No dose cap**
  - Challenging to make, requires specialized equipment



# Eribulin

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

## ARS Question 4

You have a 65 year old female with recurrent, metastatic TNBC who has relapsed 3 years after her adjuvant therapy (DDAC-T). She has significant disease burden in the liver with AST 479, ALT 581 and Tbili 5.3. She is scheduled to get a biliary stent evaluation next week, but would like to start chemotherapy tomorrow. What chemotherapy may be preferred based on toxicity and drug metabolism?

- A. Liposomal doxorubicin
- B. Carboplatin
- C. Docetaxel
- D. Ixabepilone

SELECT TARGETED AGENTS

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# Immunomodulatory Drugs (IMiDs)

- **MOA:** Not fully understood
  - Antiangiogenic
  - Immunomodulating
  - Antineoplastic
  - Inhibits inflammatory cytokine secretion
    - Inhibits TNF $\alpha$  secretion
    - Increase LF-2 and INF $\gamma$  secretion
- **Black Box Warnings**
  - Teratogenicity (**REMS program required**)
  - Thromboembolism
  - Neutropenia/thrombocytopenia (lenalidomide only)



# IMiDs

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

	<b>Bortezomib (Velcade)</b>	<b>Carfilzomib (Kyprolis)</b>	<b>Ixazomib (Ninlaro)</b>
<b>Use</b>	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
<b>Administration</b>	SQ, IV	IV	PO
<b>Dosing</b>	1.3 mg/m <sup>2</sup> days 1, 4, 8 and 11 Q21 days 1.5 mg/m <sup>2</sup> days 1, 8, 15, and 22 Q28 days	Cycle 1 20 mg/m <sup>2</sup> days 1, 2 27 mg/m <sup>2</sup> days 8, 9,15,16 Q28 days Can increase up to 56 mg/m <sup>2</sup>	4 mg Days 1, 8, and 15 Q28 days on an empty stomach
<b>PK/PD</b>	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)
<b>ADEs</b>	Fatigue, malaise, N/V, diarrhea, constipation, neutropenia, <b>thrombocytopenia, peripheral neuropathy</b> Cardiotoxicity: orthostatic hypotension, edema, CHF		
<b>Comparison</b>	<b>Most peripheral neuropathy:</b> IV > SubQ	<b>Most cardiotoxic</b> Rare: pulmonary toxicity, RPLS, TLS, acute liver	Less peripheral neuropathy
<b>Drug Interactions</b>	CYP3A4, CYP2C19	PgP	CYP3A4; PgP
<b>Pre-medications</b>		Dexamethasone 4mg PO/IV	
<b>Notes</b>		Cap BSA at 2.2 m <sup>2</sup> Give fluids prior to first cycle, then PRN	

# Daratumumab (Darzalex/Darzalex Faspro)

- **MOA:**

- IgG1k 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



# Belantamab Mafodotin (Blenrep)

- **MOA:** Antibody-drug conjugate directed at BCMA that releases a microtubule-disrupting agent (MMAF) to targeted cells.
- **Dosing:** 2.5mg/kg IV Q3weeks
  - Dose reduce to 1.9mg/kg IV Q3weeks for intolerability
- **ADEs:**
  - Thrombocytopenia, lymphocytopenia
  - Blurred vision, decreased visual acuity
  - Increased creatinine
  - Increased LFTs
- **Black Box Warning/REMS Program**
  - Patients must have ophthalmic exam prior to each dose

# ARS Question 5: Patient Case

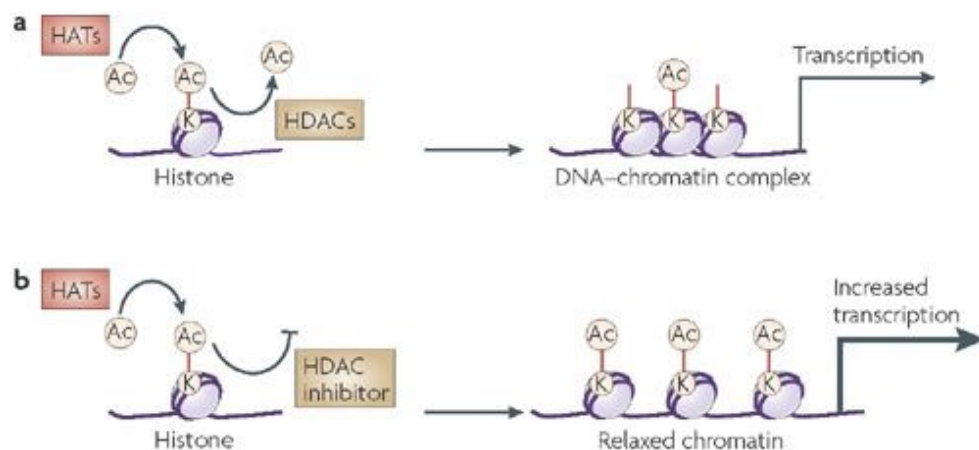
- 68 year old man with IgG lambda multiple myeloma
- **At diagnosis:**
  - MSpoke 4.2 g/dL
  - Kappa free light chains 1.42 mg/dL
  - Lambda free light chains 122 mg/dL
  - Free light chain ratio of 29.05
- 6 cycles of VRD (bortezomib, lenalidomide, and dexamethasone)
- MSpoke plateaued at 2.1 g/dL
- ADRs on VRD: neuropathy, which lead to delays in cycles.
- **PMH:**
  - Heart failure with reduced ejection fraction
  - Diabetes (well controlled with medication and diet)
  - Hyperlipidemia.
- **Current medications:**
  - Metformin, metoprolol, lisinopril, atorvastatin, gabapentin, and furosemide as needed. What would you recommend as second line therapy for AB?

## ARS Question 5:

- What would you recommend as second line therapy for AB?
- A. Carfilzomib, pomalidomide, dexamethasone (KRd)
- B. Daratumumab, lenalidomide, dexamethasone (DRd)
- C. Daratumumab, bortezomib, dexamethasone (DVd)
- D. Selinexor and dexamethasone

# 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



# FLT3 Inhibitors

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

# IDH Inhibitors

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

# CD-19 Directed Antibodies

	Loncastuximab Tesirine (Zynlonta)	Tafasitamab (Monjuvi)
<b>Use</b>	R/R LBCL	R/R DLBCL
<b>Dose</b>	C1-2: 0.15mg/kg IV Q3weeks C3+: 0.075mg/kg IV Q3weeks	12mg/kg C1: Days 1, 4, 8, 15, 22 Q28Days C2-3: Days 1, 8, 15, 22 Q28Days C4+: Days 1, 15 Q28Days
<b>Common Toxicities</b>	Neutropenia, thrombocytopenia, and anemia	
	Increased LFTs Increased serum glucose Edema, cutaneous reactions	Infections Infusion reactions
<b>Notes</b>	Use adjusted body weight for BMI $\geq 35$	Combined with lenalidomide

# Chimeric Antigen Receptor T Cells

CD19 targeted	Tisagenlecleucel (Kymriah)	Axicabtagene ciloleucel (Yescarta)	Brexucabtagene autoleucel (Tecartus)	Lisocabtagene maraleucel (Breyanzi)
Use	ALL (age <26), DLBCL	FL, LBCL	MCL	LBCL
ADEs	Cytokine release syndrome (CRS) Neurotoxicity Anemia, neutropenia, lymphocytopenia, thrombocytopenia			
Costim. Domain	4-1BB	CD28	CD28	4-1BB

BCMA targeted	Idecabtagene vicleucel (Abecma)
Use	Multiple myeloma
ADEs	Cytokine release syndrome (CRS) Neurotoxicity Anemia, neutropenia, lymphocytopenia, thrombocytopenia
Costim. Domain	4-1BB



# Non-Malignant Heme Drugs

- **Caplicizumab-yhdp (Cablivi)**

- **Indication:** Thrombotic thrombocytopenia 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

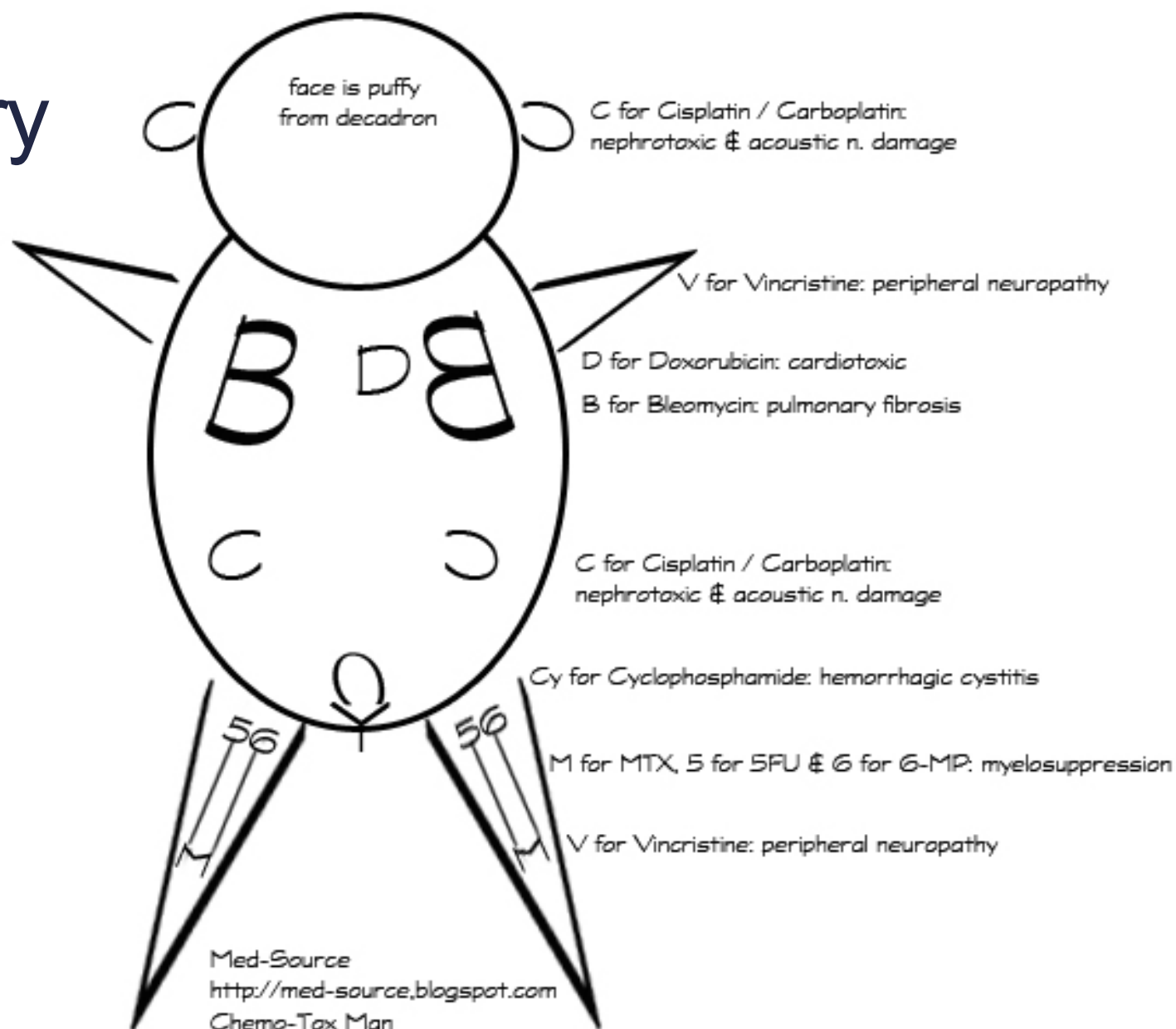
- **Givosiran (Givlaari)**

- **Indication:** Acute hepatic porphyria
- **Dose:** 2.5 mg/kg SubQ monthly
- **MOA:** Causes degradation 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



# Thank you!

## Acknowledgements:

- Tara L. Chen, PharmD, BCOP
- Helen Marshall, PharmD, BCPS, BCOP
- Laura Alwan, PharmD, BCOP
- Amy Indorf, PharmD, BCOP



# APPENDICES

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## 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

## 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

# 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