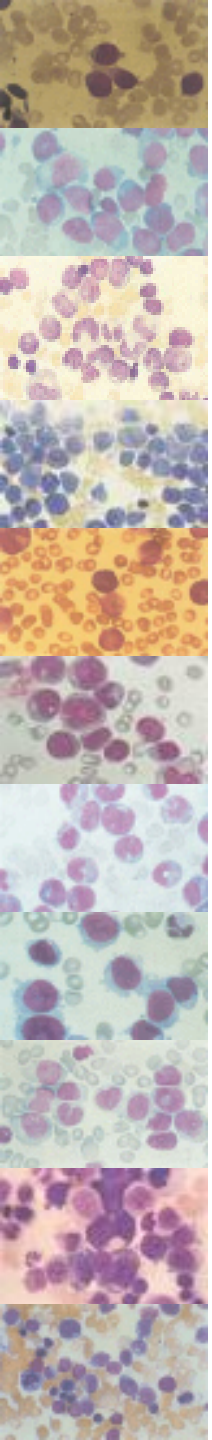
Curso: Fortalecimiento de la Gestión del Cuidado de Enfermería Oncológica

Quimioterapia: Concepto, Clasificación, Mecanismo de Acción y Farmacología

Dr. Henry L Gomez
Instituto Nacional de Enfermedad Neoplásicas
Lima, 24 de Abril, 2014

Historia

- La quimioterapia se introdujo en la quinta y sexta del siglo XX
- Paul Erlich, fue quien acuño este termino, desarrollando drogas en modelos animales
- Segunda guerra mundial, con el uso de alquilantes, observaron regresión de neoplasias linfoides
- Estos hechos recién fueron publicados en 1946 por Marchall.

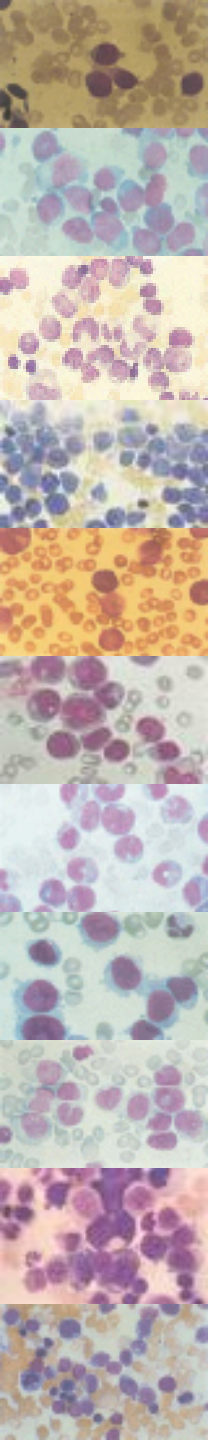


History of Chemotherapy

- Era of modern chemotherapy began in early 1940s
- **Goodman and Gilman** first administered nitrogen mustard to patients with lymphoma
  - nitrogen mustard was developed as a war gas rather than as a medicine
  - toxic effects on the lymphatic system led to clinical trials

Papel de la Quimioterapia

- Terapia de induccion para enfermedad avanzada
- Adyuvante a tratamientos locales
- Neoadyuvante: tratamiento primario en pacientes de con una neoplasia localizada
- Regional, colocación directa en regiones especificas



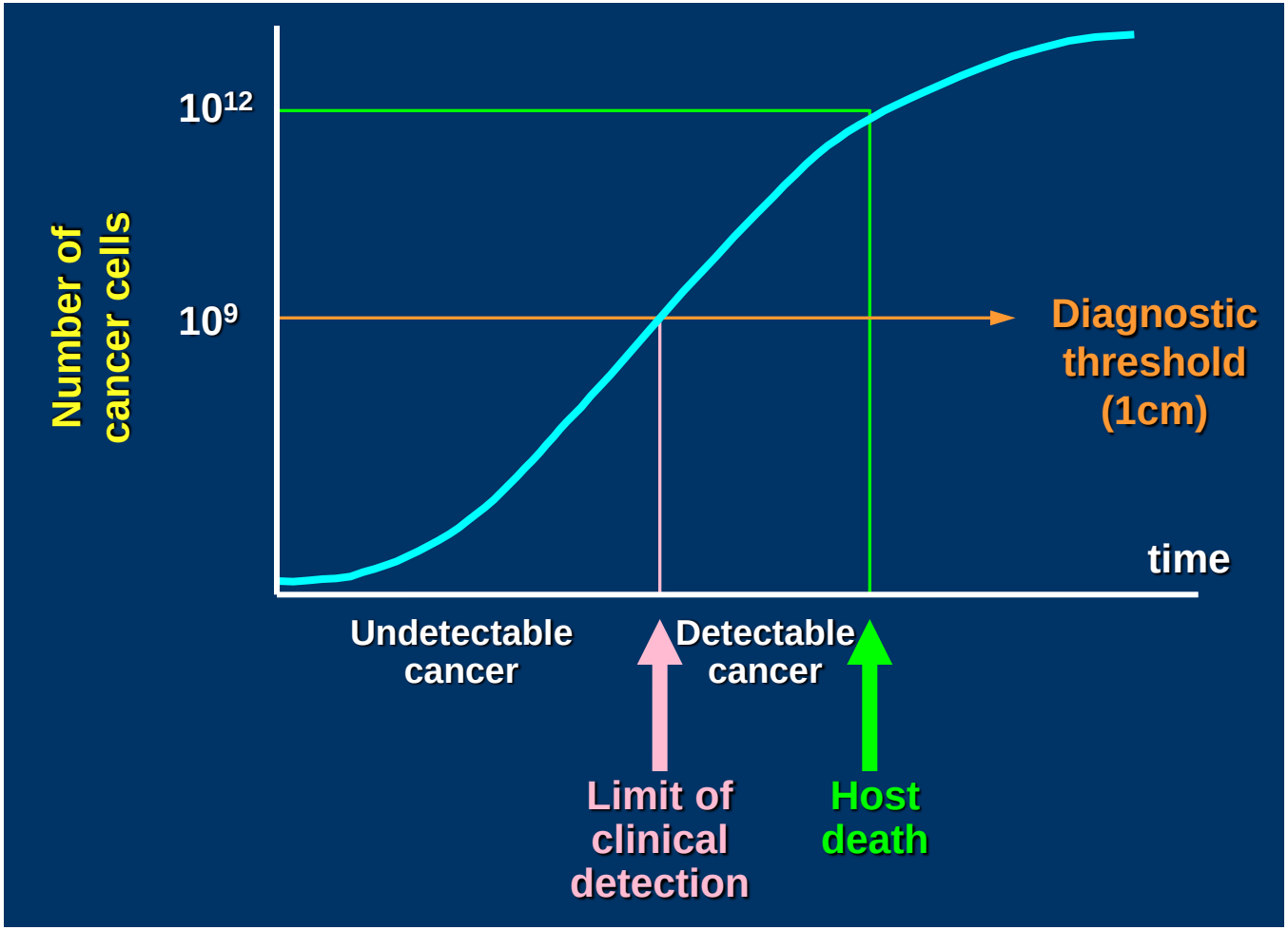
Chemotherapy

- Chemotherapy attacks tumors at the cellular level by interrupting processes or inhibiting substances necessary for cellular replication and life
- During the cell cycle, there is replication of the entire genome and division of the cell into genetically identical daughter cells
- Goals of Cancer Chemotherapy
  - Cure
  - Prolong survival
  - Palliation
  - Radiosensitive

ONCOLOGY

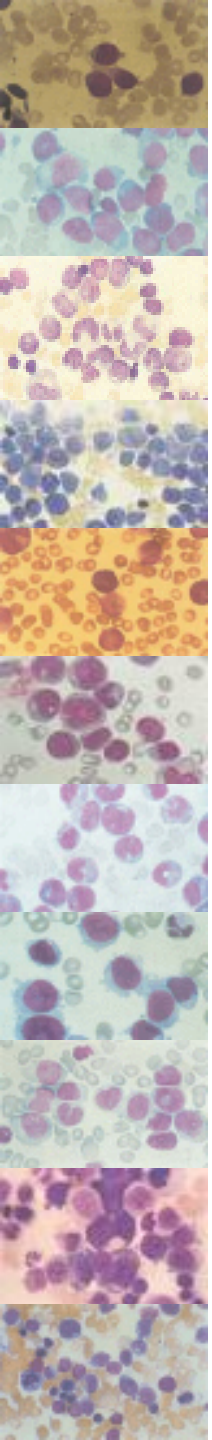
Cancer biology

Tumor growth and detection



Principios del Uso de Combinaciones de Quimioterapia

- Con excepciones raras con ETG, donde el estándar terapéutico es mono droga,
- La combinación de citostaticos es la forma mas extendida de uso en tumores solidos, con el fin de vencer la resistencia
- Otra observación, las drogas seleccionadas deberían ser las mas efectivas, pero su perfil de toxicidad no se superpusieran
- El intervalo de tratamientos giro en relación a la recuperacion medular, principalmente

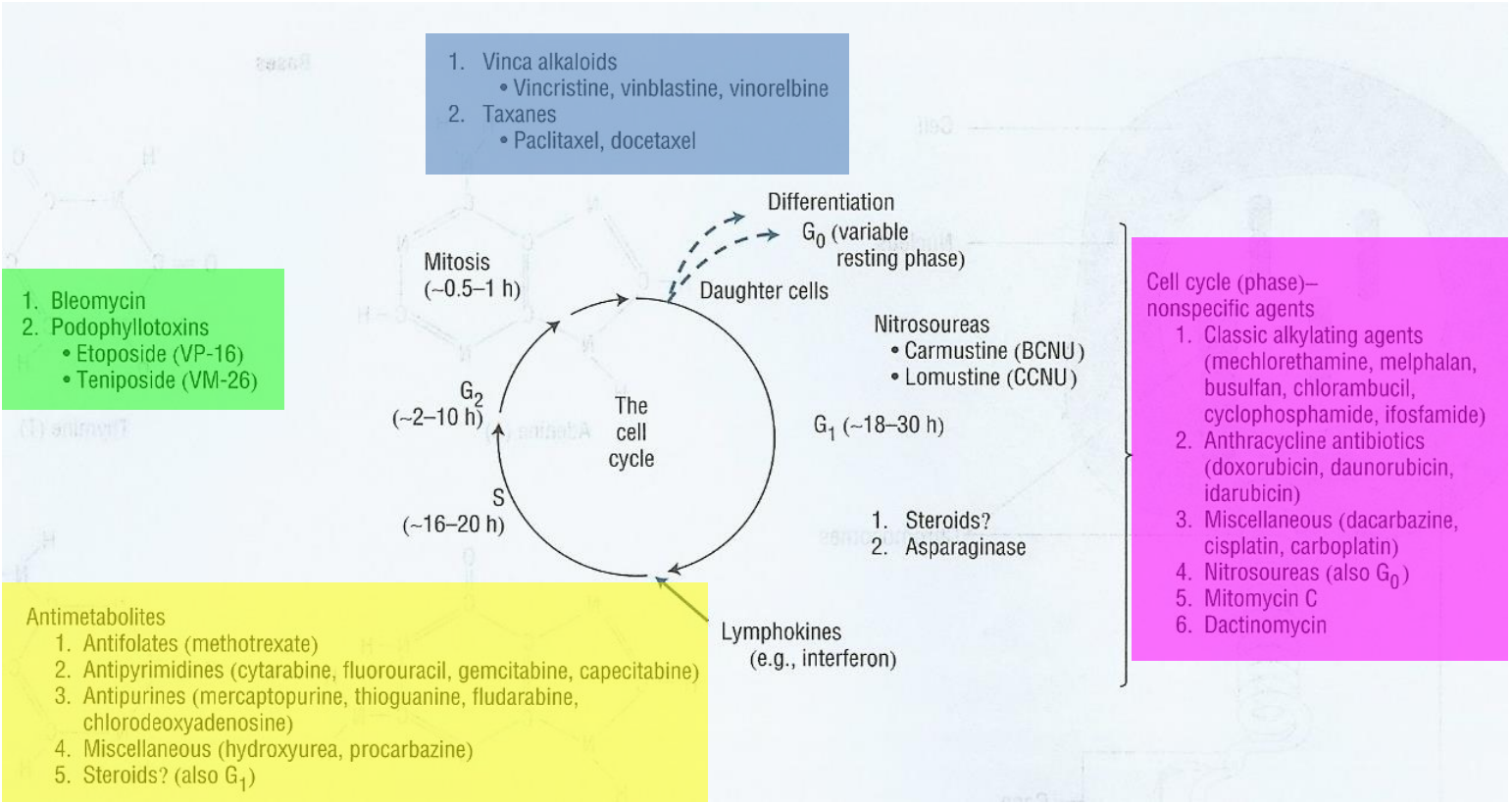


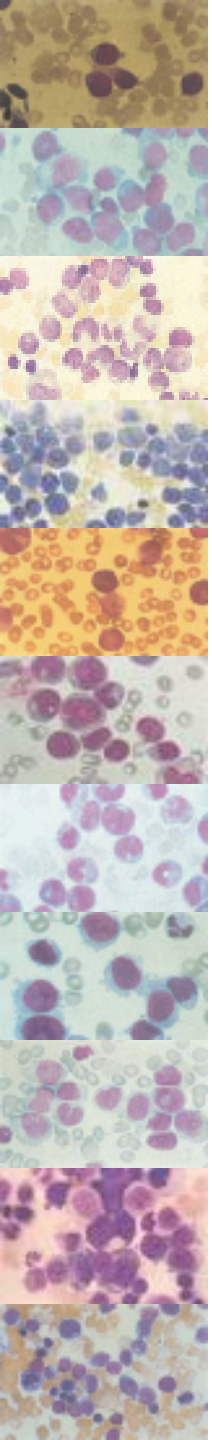
The Cell Cycle

- G_1 phase: cell prepares for DNA synthesis
- S phase: cell generates complete copy of genetic material
- G_2 phase: cell prepares for mitosis
- M phase: replicated DNA is condensed and segregated into chromosomes
- G_0 phase: resting state

Conventional Chemotherapy

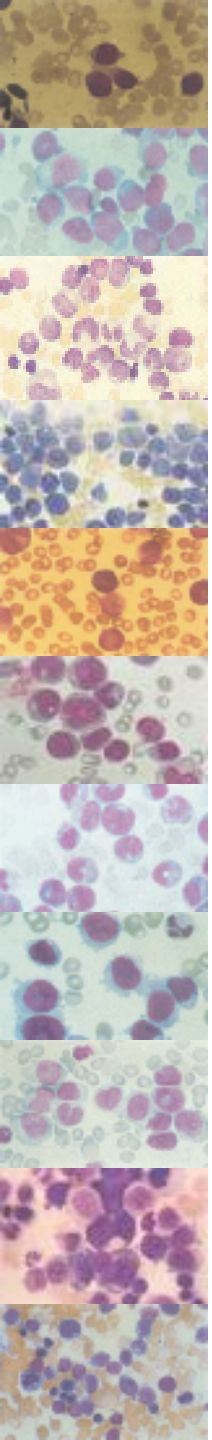
- Backbone of cancer chemotherapy regimens
- Cytotoxicity is not selective





Chemotherapy

- **Cell cycle phase – specific**
  - agents with major activity in a particular phase of cell cycle
  - schedule dependent
- **Cell cycle phase – nonspecific**
  - agents with significant activity in multiple phases
  - dose dependent



Chemotherapy Classes

- **Alkylating agents**
  - nitrogen mustards
  - thiotepa, busulfan
  - nitrosoureas, mitomycin
  - procarbazine, dacarbazine
- **Taxanes**
  - paclitaxel, docetaxel
  - nab-paclitaxel
- **Topoisomerase II inhibitors**
  - etoposide
- **Platinum Complexes**
  - cisplatin, carboplatin
  - oxaliplatin
- **Anthracyclines**
  - doxorubicin, daunorubicin
  - idarubicin, mitoxantrone
- **Antimetabolites**
  - methotrexate
  - purine antagonists
  - pyrimidine antagonists
- **Tubulin interactive agents**
  - vincristine, vinblastine
- **Miscellaneous agents**
  - bleomycin
  - asparaginase
  - hydroxyurea

ONCOLOGY

Principles of chemotherapy

Side effects of chemotherapy

Mucositis

Nausea/vomiting

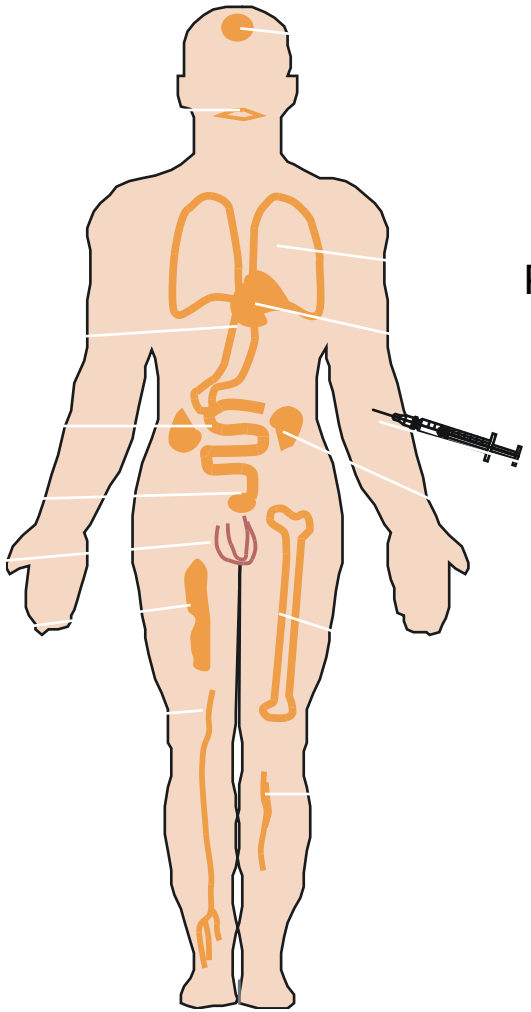
Diarrhea

Cystitis

Sterility

Myalgia

Neuropathy



Alopecia

Pulmonary fibrosis

Cardiotoxicity

Local reaction

Renal failure

Myelosuppression

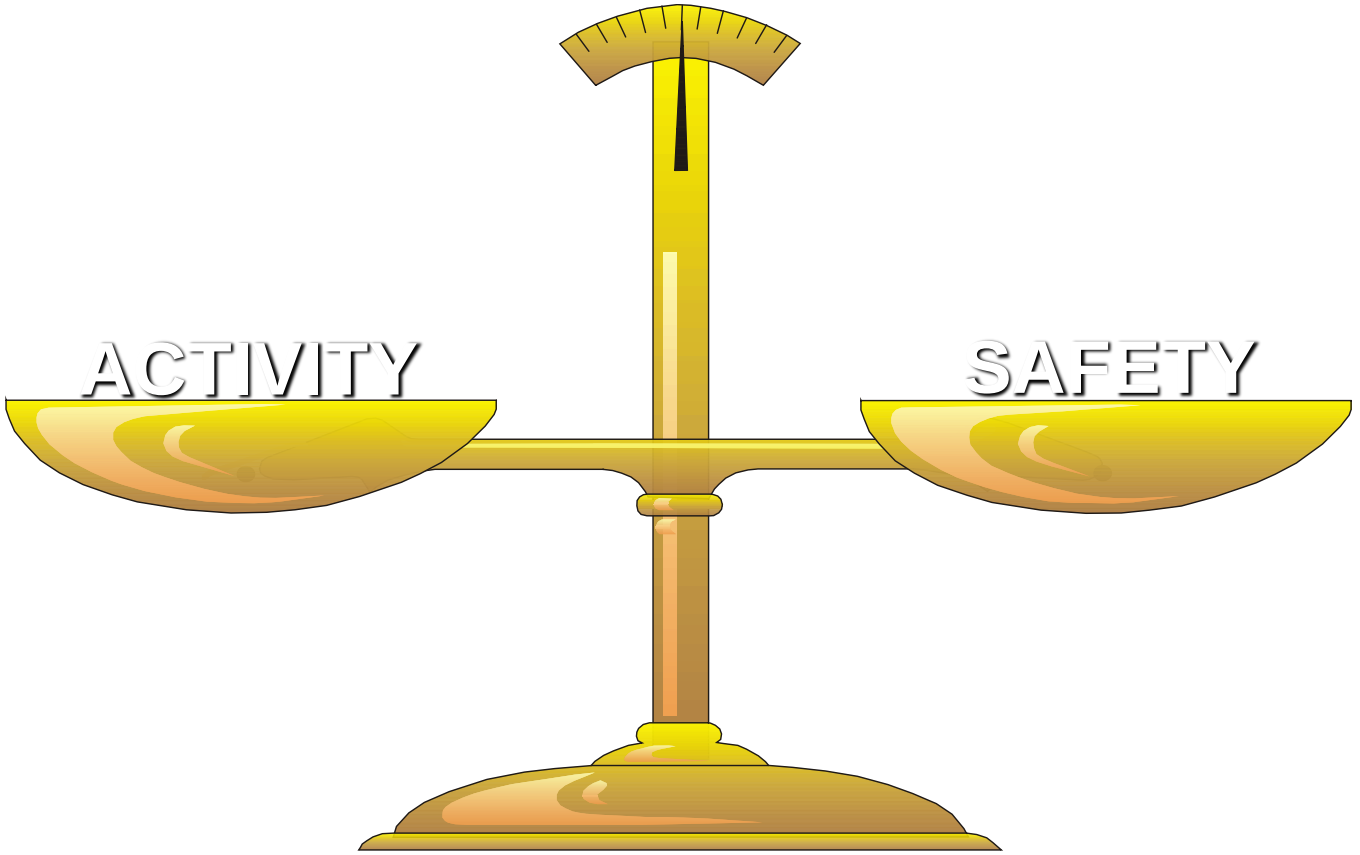
Phlebitis

ONCOLOGY

Principles of chemotherapy

Aim of combination therapy

INCREASED EFFICACY



La Hipótesis de Goldie – Coldman (1979)

- Predice que la resistencia a las drogas, debe estar presente aun en los pequeños tumores.
- La máxima posibilidad de curación ocurre cuando todas las drogas activas disponibles son administradas simultáneamente.

Principles of combination chemotherapy
Freireich EJ. MD

- Effective chemotherapy
- Non-overlapping toxicities
- Drug synergy
- Drugs without anti-tumor properties in combination

Meta-analysis of Randomized Trials of Chemotherapy for Advanced Breast Cancer

Comparison	Death Hazard Ratio	
Multiple vs. single agent	0.82	(0.75-0.90)
Anthracycline vs non-anthr.	0.84	(0.00-0.00)
Higher vs lower dose	0.90	(0.83-0.97)
With vs without hormonal Rx	0.99	(0.92-1.07)

Combinations used less active agents, no taxanes!

Fossati et al JCO 1998
Fossati et al JCO 2000

La Hipótesis de Day – Norton (1986)

- Es conocida también como la teoría Gompertzian de cinética de crecimiento celular.
- Pequeños tumores contienen varias clonas de células con diferentes tasa de proliferacion (alta – moderada), con diferente sensibilidad a la quimioterapia.

Treatment

N=2,005

T0-3, N1-2, M0

RANDOMIZE

Sequential (36 wks)
A x 4 q 3 wk ⇒ P x 4 q 3 wk ⇒ C x 4 q 3 wk

***Dose-dense* Sequential (24 wks)**
A x 4 q 2 wk ⇒ P x 4 q 2 wk ⇒ C x 4 q 2 wk
+ G-CSF

Concurrent (24 wks)
AC x 4 q 3 wk ⇒ P x 4 q 3 wk

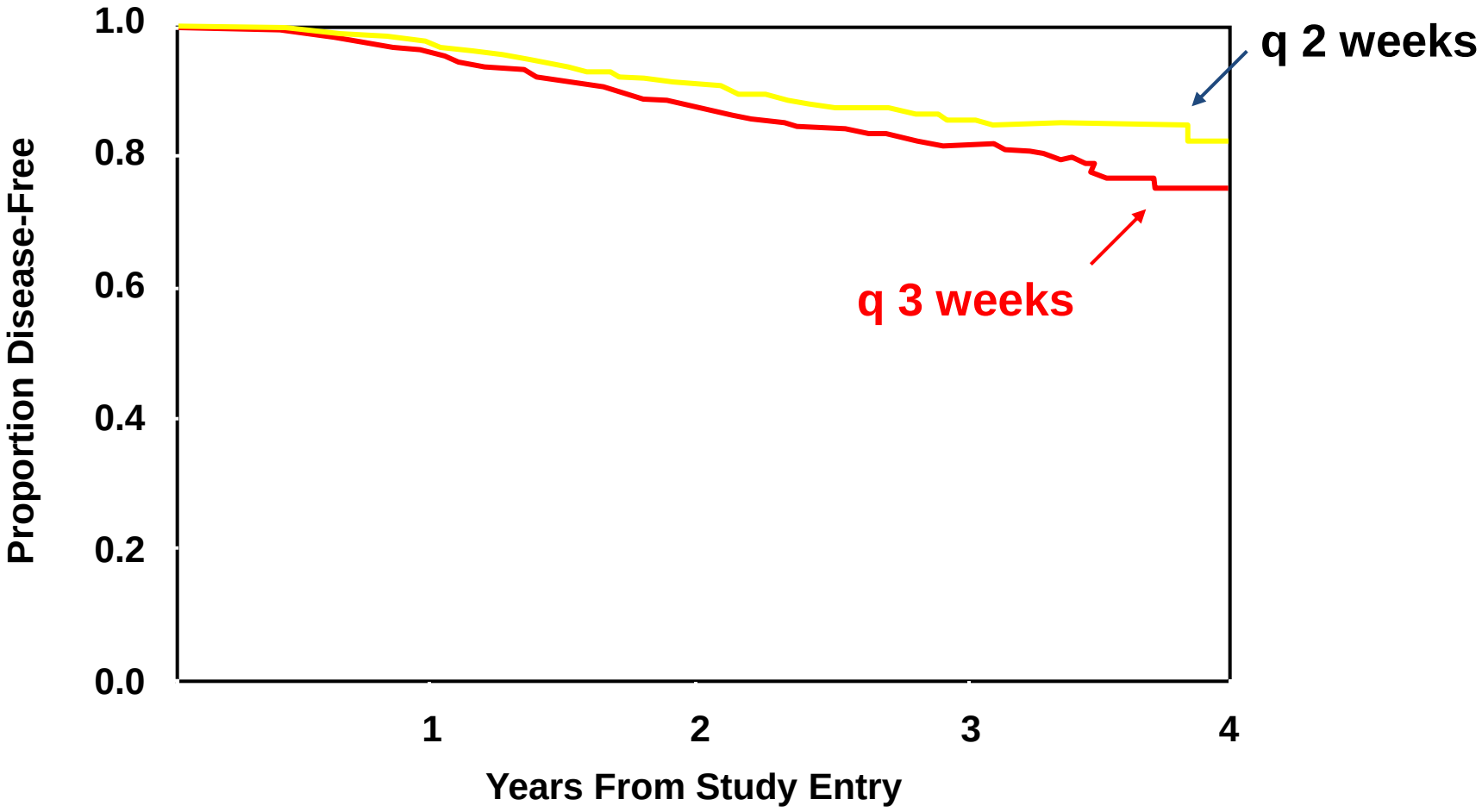
***Dose-dense* Concurrent (16 wks)**
AC x 4 q 2 wk ⇒ P x 4 q 2 wk
+ G-CSF

A= doxorubicin 60 mg/m^2
P= paclitaxel 175 mg/m^2 over 3 h
C= cyclophosphamide 600 mg/m^2

*** Tamxifen if Postmenopausal or ER+ and Premenopausal**

Citron M, et al. *JCO* 2003; Vol 21, No 7 (Apr 1).

Disease-Free Survival
By Density



q 2 wks	N=988	Events=136
q 3 wks	N=985	Events=179

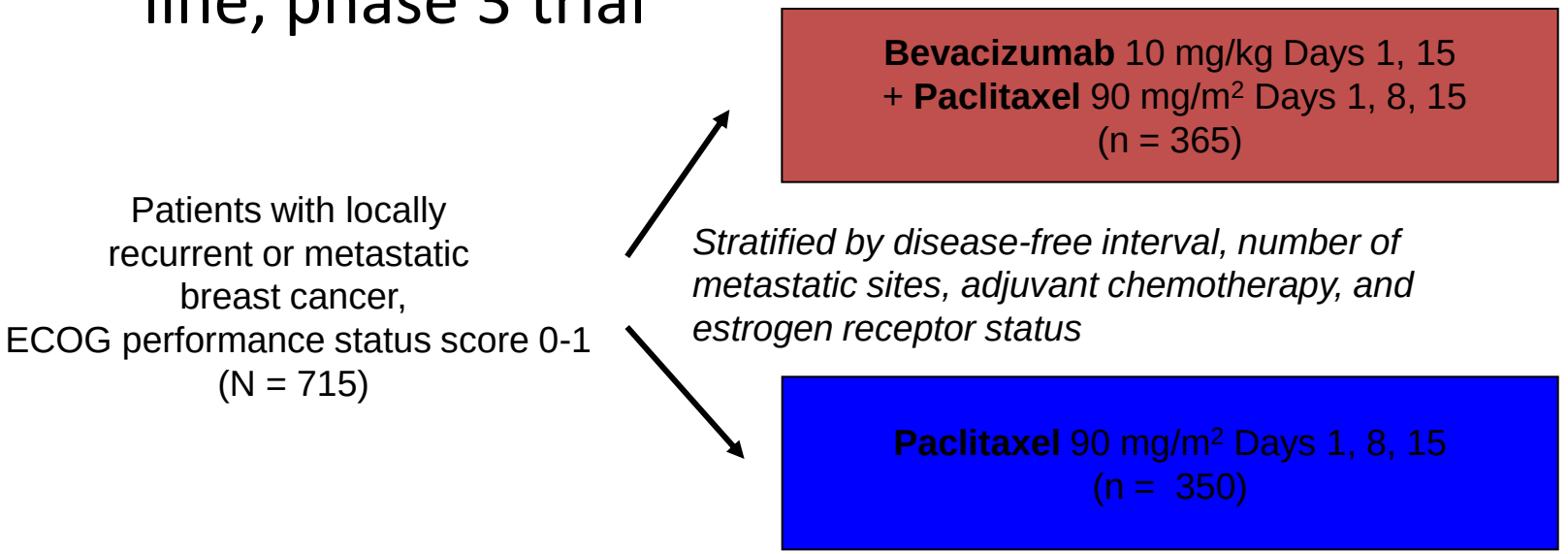
Citron M, et al. *JCO* 2003; Vol 21, No 7 (Apr 1).

La Teoría de Pusztai (1998)

- Los tumores están formados de poblaciones células heterogéneas y en términos de sensibilidad existen tres tipos de células:
  - Fisiológicamente resistente
  - Sensible
  - Patológicamente resistente

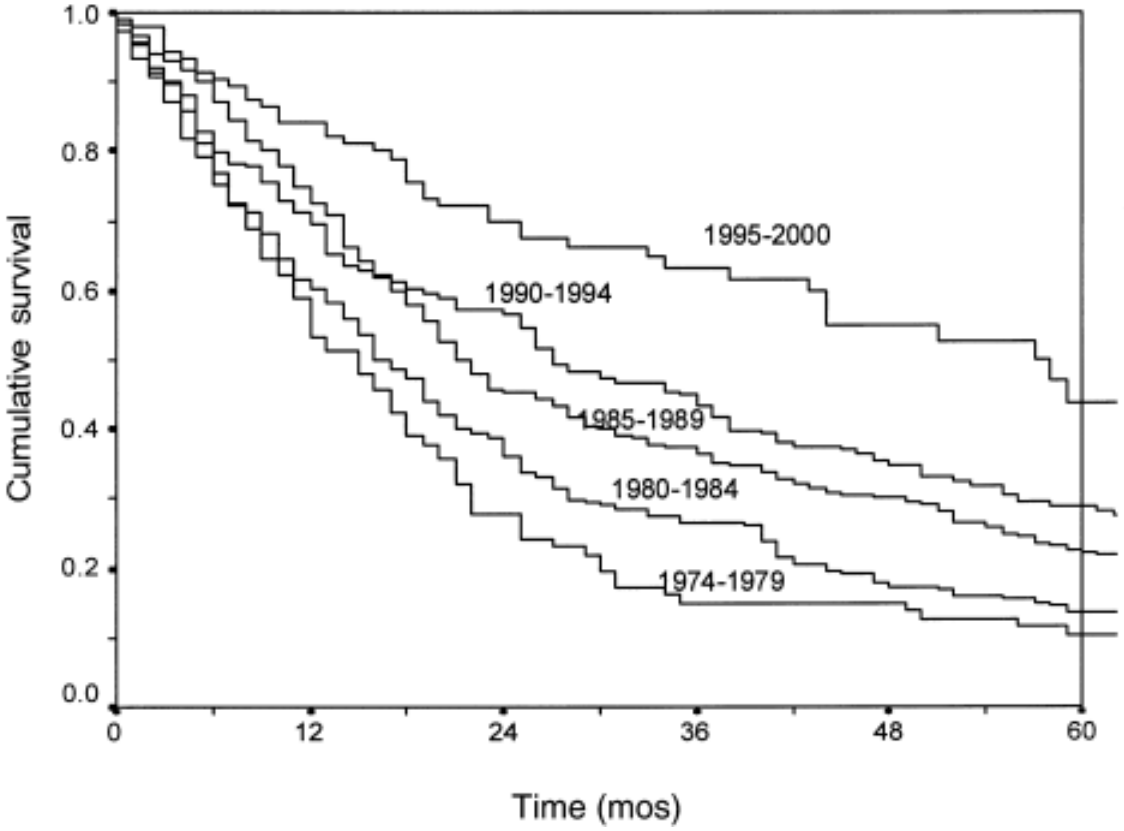
Bevacizumab ± Paclitaxel for Locally Recurrent or Metastatic Disease

- Eastern Cooperative Oncology Group (ECOG) 2100 trial
  - First planned interim analysis of randomized, first-line, phase 3 trial

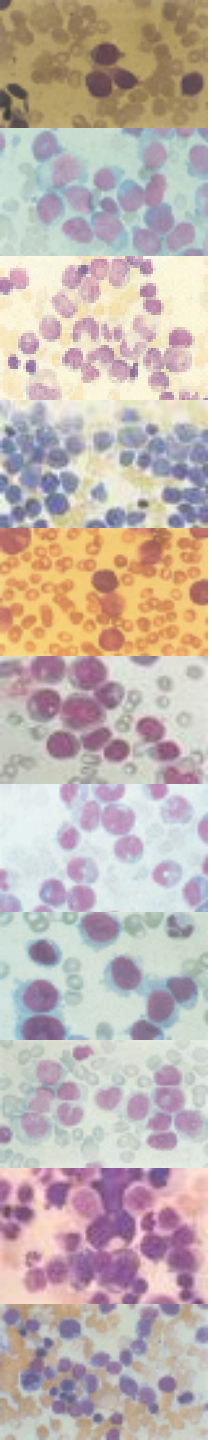


Miller et al. ASCO 2005. Oral presentation during symposium, Advances in Monoclonal Antibody Therapy for Breast Cancer.

Experiecia MDACC

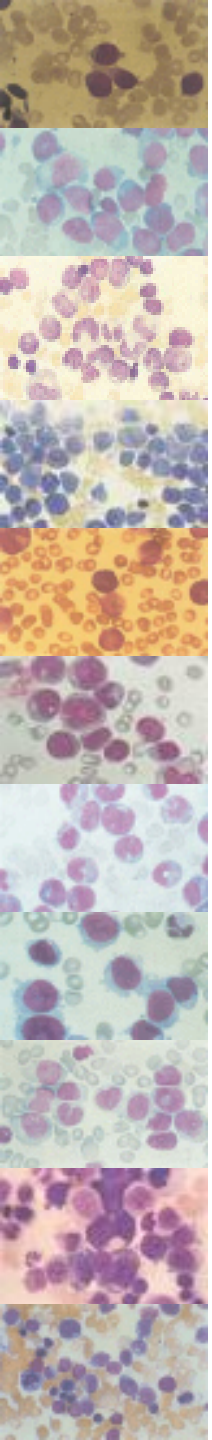


Giordano et al, Cancer 100:44-52, 2004



Chemotherapy Toxicity

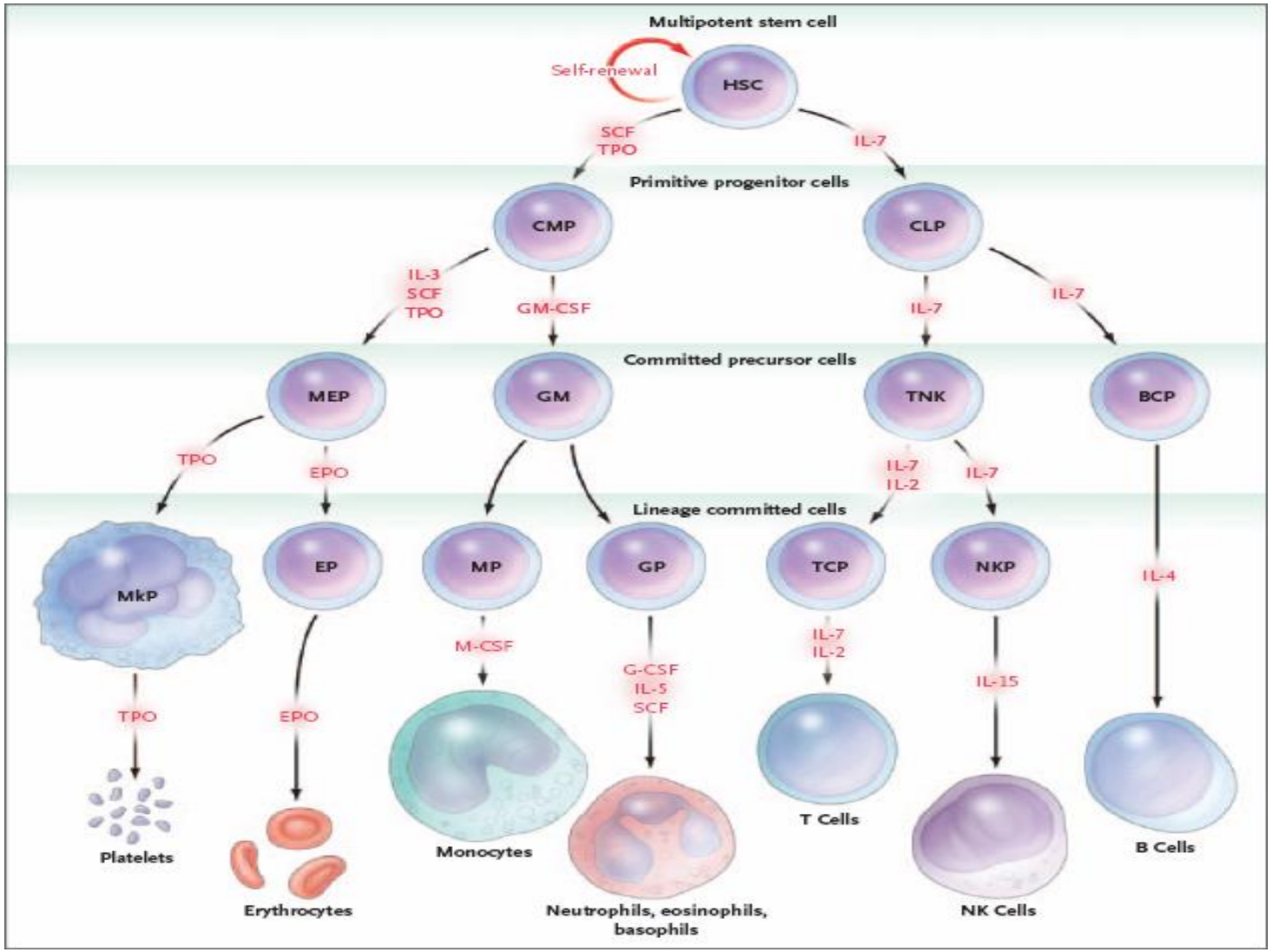
- Usually reflected by mechanism of action of drug
- Toxicity depends on many factors
  - Drug dosing and schedule (DLT)
  - Patient
  - Disease
- Toxicity not always a class effect
- Chemotherapy regimens usually combine drugs that have different



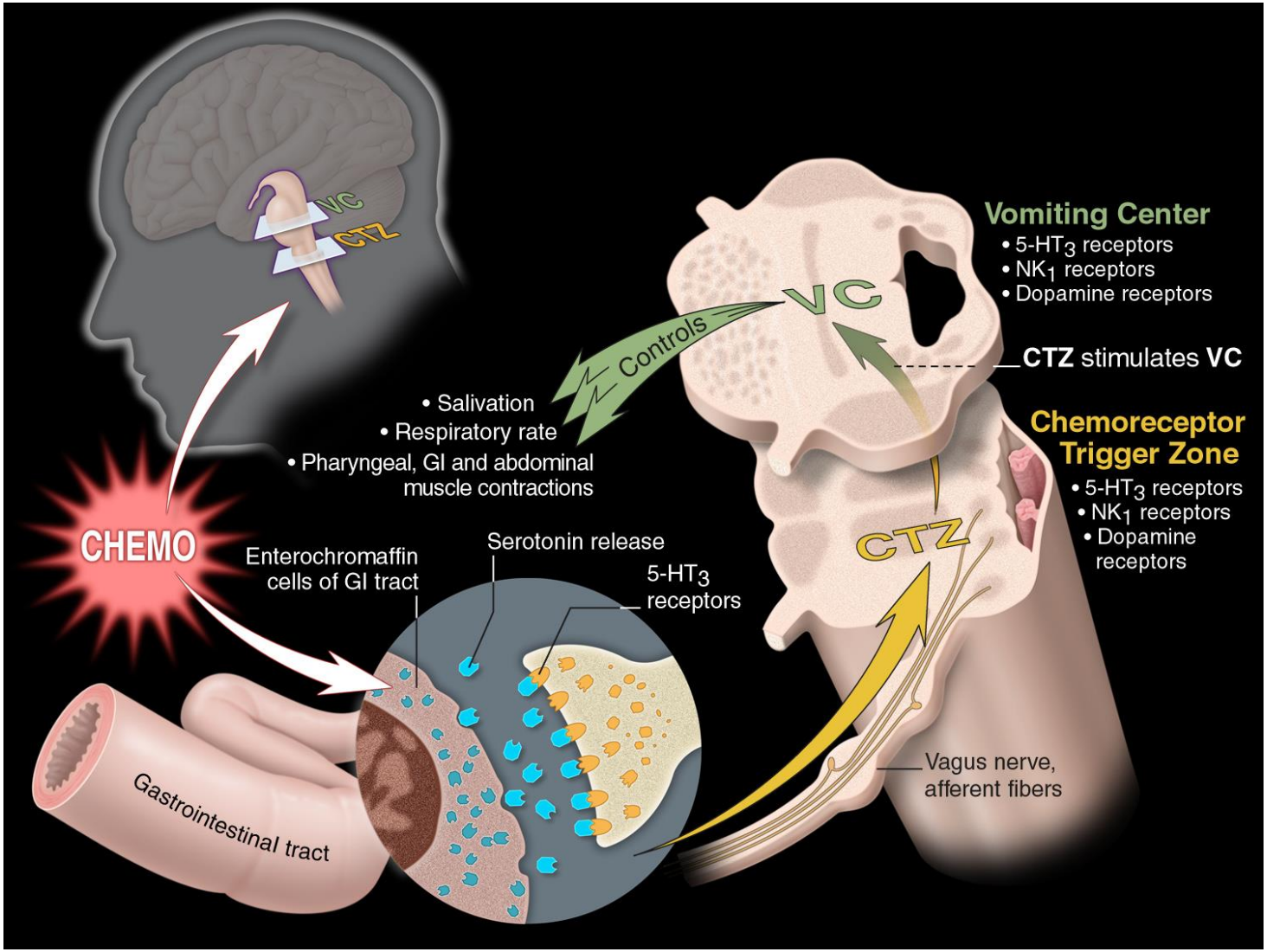
Common Toxicities

- Most chemotherapy drugs are active in cells that are rapidly multiplying
  - Chemotherapy may not be very active in indolent or slow growing tumors
- Because of cytotoxic action on rapidly dividing cells they are toxic to normal cells that are actively multiplying
  - Bone marrow, GI tract, hair follicles are all rapidly multiplying
- Thus common toxicity of chemo agents are -
  - Neutropenia, anemia, and thrombocytopenia (collectively called myelosuppression or bone marrow suppression)
  - Mucositis, diarrhea (GI toxicity)
  - Nausea and vomiting
  - Alopecia
  - Sterility/Infertility (especially sterility in males)
- Common Toxicity Criteria Grading System (CTC)
  - Grade 0 – 4

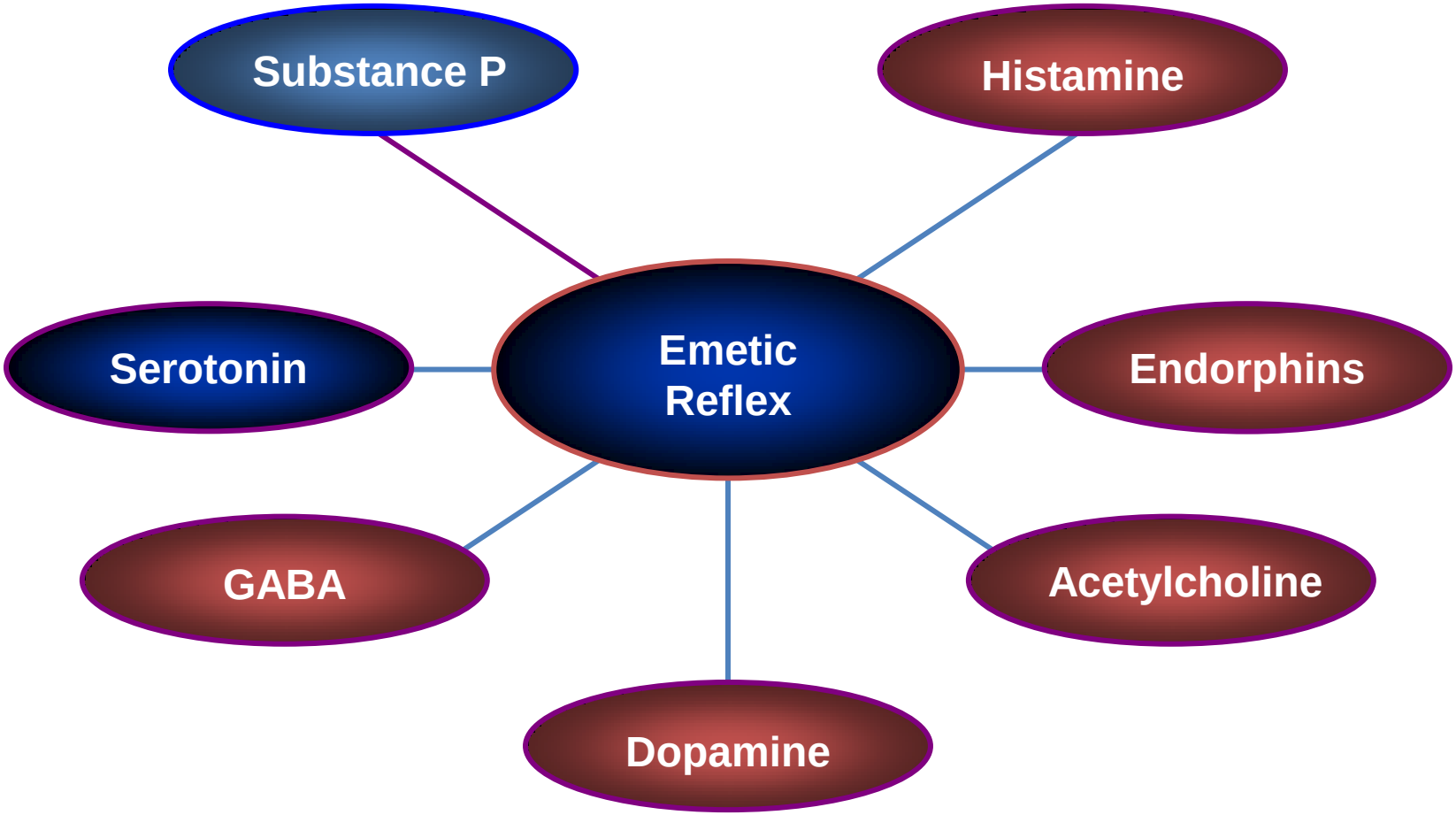
Myelosuppression

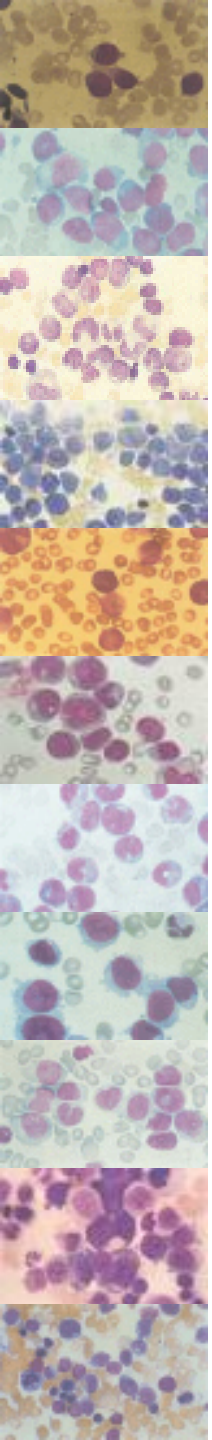


Nausea and Vomiting



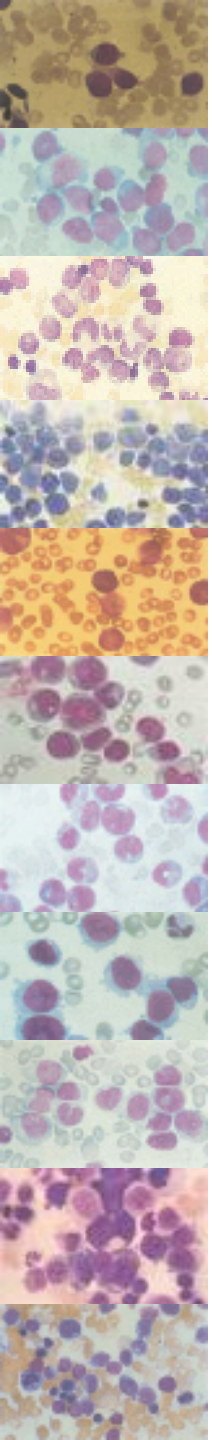
Targeting Neurotransmitters





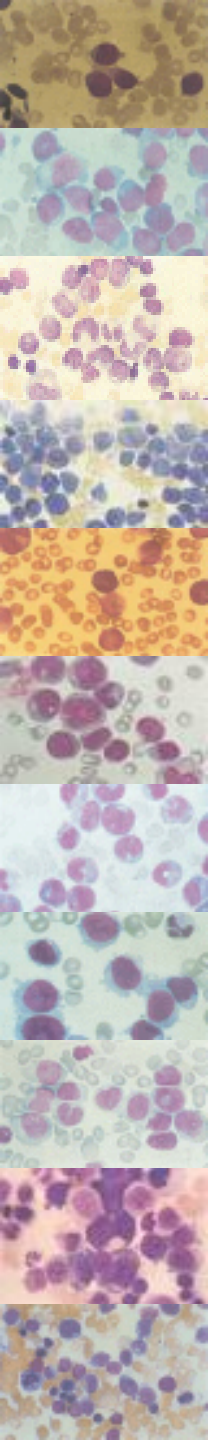
Chemotherapy Toxicity

- **Neurologic**
  - CNS: cytarabine, methotrexate, ifosfamide
  - Peripheral: paclitaxel, oxaliplatin, vincristine
- **Gastrointestinal**
  - Nausea and vomiting: cisplatin, doxorubicin, cyclophosphamide
  - Mucositis: methotrexate, melphalan, etoposide, 5-FU
- **Pulmonary**
  - Methotrexate, bleomycin
- **Cardiovascular**
  - Anthracyclines



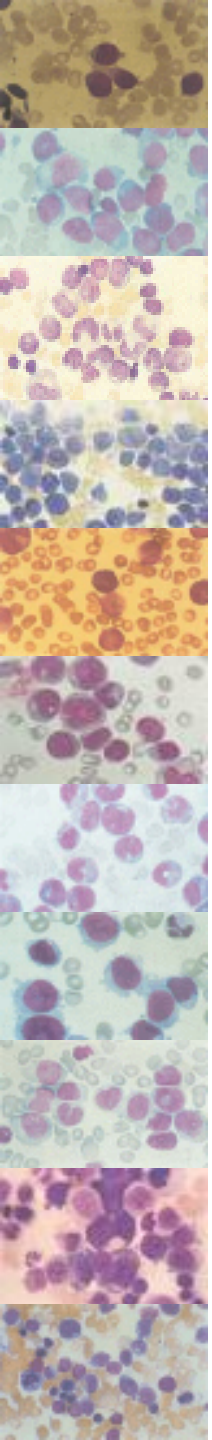
Chemotherapy Toxicity

- **Hepatic**
  - busulfan
- **Metabolic**
  - **Ifosfamide, cisplatin**
- **Renal**
  - Hemorrhagic cystitis: cyclophosphamide, ifosfamide
  - Renal failure: cisplatin
- **Dermatologic**
  - Hand-foot syndrome: 5-FU, capecitabine, cytarabine
- **Immune System**
  - Immunosuppression: fludarabine, cyclophosphamide, steroids
  - Hypersensitivity: paclitaxel, asparaginase, bleomycin



Miscellaneous Toxicity

- Asparaginase
  - Coagulation disorders
  - Hyperlipidemia
  - Hyperglycemia
  - Pancreatitis
- Etoposide
  - Hypotension, flushing (infusion-related)
- Irinotecan
  - Acute and delayed diarrhea (SN-38 metabolite)

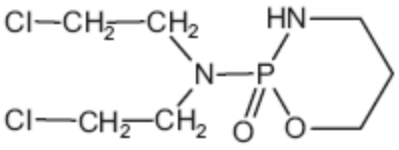


Secondary Leukemias

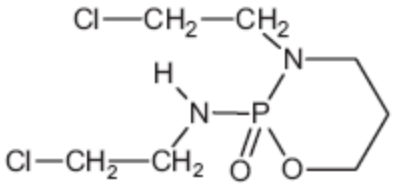
- Leukemias secondary to chemotherapy agents have poor prognosis.
- Secondary to alkylating agents
  - Most often occur after 5 – 7 years
  - Often have MDS preceding leukemia
  - Frequently FAB class M1 or M2
  - Alterations of chromosomes 5 and/or 7 in 60% – 90% cases
- Secondary to topo II inhibitors:
  - Diagnosed 2 -3 yrs after tx
  - Most often FAB class M4 or M5
  - Frequent translocation of chromosome 11 (11q23) t(11;19)(q23;p13)

Alkylating Agents

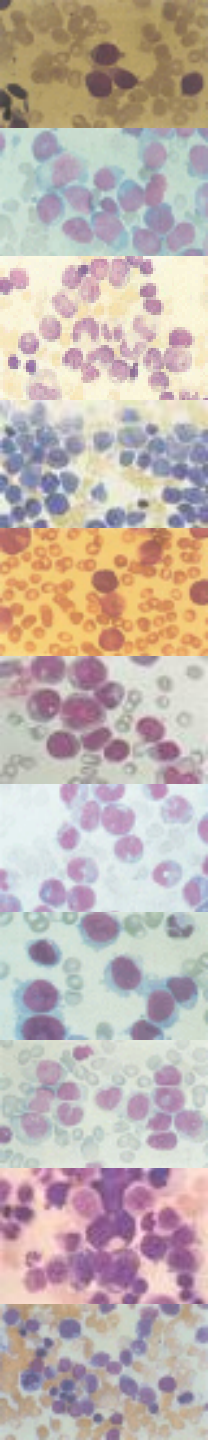
- Main effect is on DNA synthesis with most cytotoxicity to rapidly proliferating cells



Cyclophosphamide

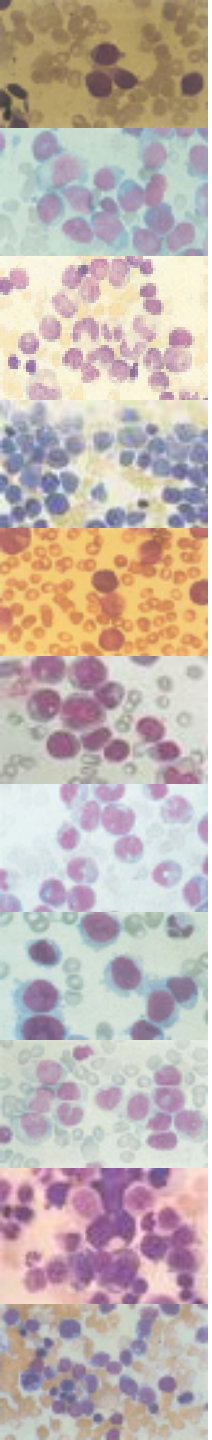


Ifosfamide



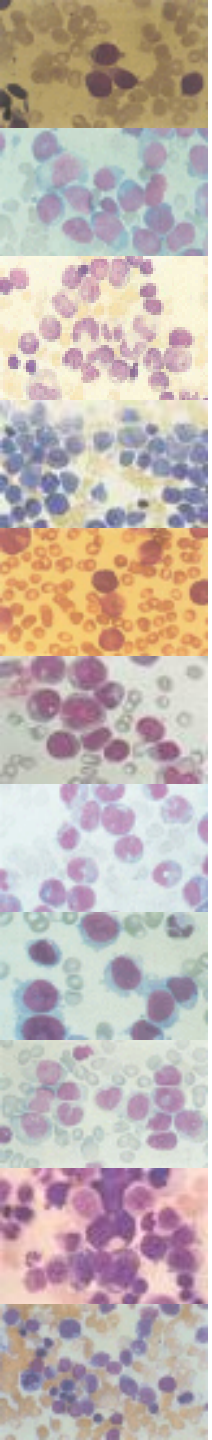
Alkylating Agents

- Mechanism of action
  - act as bifunctional alkylating agents following metabolic activation and formation of mustards
    - mustards react with the N7 atom of purine bases (guanine)
    - these DNA adducts go on to form cross-links through reaction of the second arm of the mustard
  - prevent cell division by cross-linking DNA strands
    - intra- and interstrand cross-links
    - cell continues to synthesize other cell constituents, such as RNA and protein, and an imbalance occurs and the cell dies
    - if these modifications in the nucleic acid structure are compatible with cell life (after DNA repair), mutagenesis and carcinogenesis result



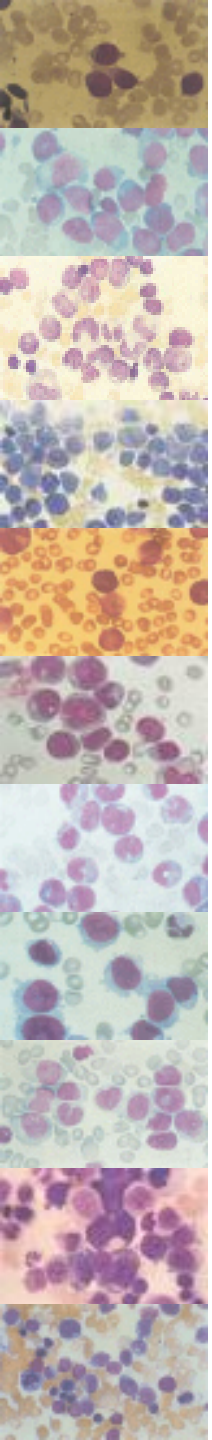
Cyclophosphamide and Toxicity

- Myelosuppression
  - principle dose-limiting toxicity
  - primarily leukopenia
- Hemorrhagic cystitis
  - acrolein metabolite
  - associated with high-dose therapy
  - more common in poorly hydrated or renally compromised patients
  - onset may be delayed from 24 hours to several weeks
  - manifests as gross hematuria
  - aggressive hydration required with high dose therapy
  - mesna administration
  - management: increase IVF, mesna, total bladder irrigation



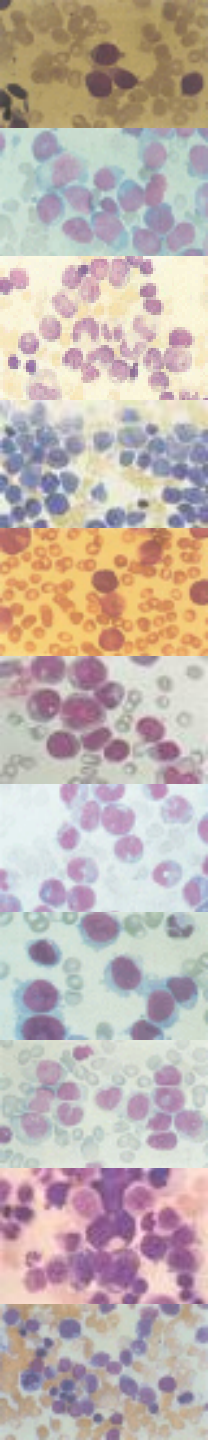
Cyclophosphamide Toxicity

- Syndrome of inappropriate antidiuretic hormone
- Alopecia
- Highly emetogenic if $\geq$ 1500 mg/m^2
- Cardiotoxicity
  - associated with high-dose therapy
  - Involves endothelial injury producing hemorrhagic necrosis
  - Decline in left ventricular systolic function



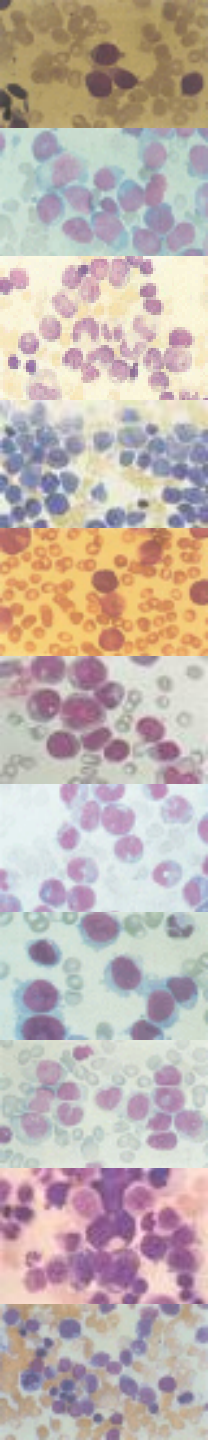
Ifosfamide Toxicity

- Hemorrhagic cystitis
  - excretion of acrolein into the urinary bladder
  - greater with bolus regimen
  - higher after ifosfamide that after equivalent doses of cyclophosphamide
  - symptoms of dysuria and urinary frequency
  - mesna binds acrolein
  - routinely recommended to protect against urothelial toxicity
  - treatment of hemorrhagic cystitis requires evacuation of clots and continuous bladder irrigation; instillation of 1% alum, prostaglandins, or high-dose tranexamic acid have been



Ifosfamide Toxicity

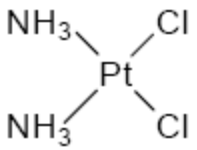
- hematologic toxicity
  - leukopenia
  - the principal dose-limiting toxicity of ifosfamide
    - white blood cell nadirs usually occur between days 8 to 13 of the treatment cycle
    - recovery will usually be complete by day 17 or 18 of the treatment cycle
- neurotoxicity
  - chloroacetaldehyde metabolite penetrates the BBB well after systemic administration
  - CNS toxicity occurring in 10–40% of the patients receiving high doses of the drug
  - encephalopathy is manifested by cerebellar ataxia, mental confusion, complex visual hallucinations
  - methylene blue as an effective treatment for ifosfamide-induced encephalopathy is controversial



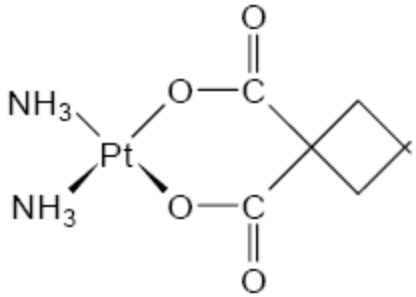
Ifosfamide Toxicity

- Fanconi syndrome
  - impairment of proximal tubule function, including glucose, protein, phosphate, bicarbonate and amino acid transport
  - generally irreversible, long-lasting and potentially progressive
  - manifested as polyuria, metabolic acidosis, and renal phosphate wasting
- Nausea and vomiting
- Alopecia
- Hepatic enzyme elevations
- Cyclophospamide and ifosfamide have little cardiac toxicity at standard doses
  - at high doses such as those used for bone marrow ablation, can cause severe myocarditis, exudative pericarditis, myocardial depression, arrhythmias

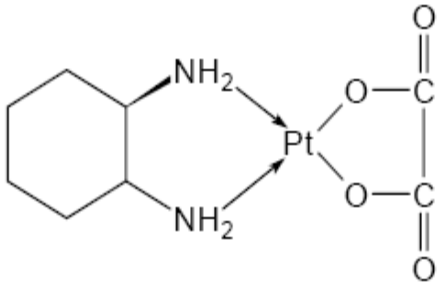
The Platinums



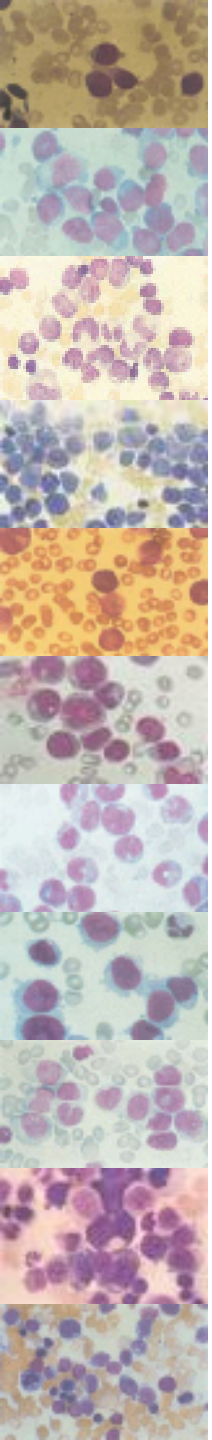
Cisplatin



Carboplatin

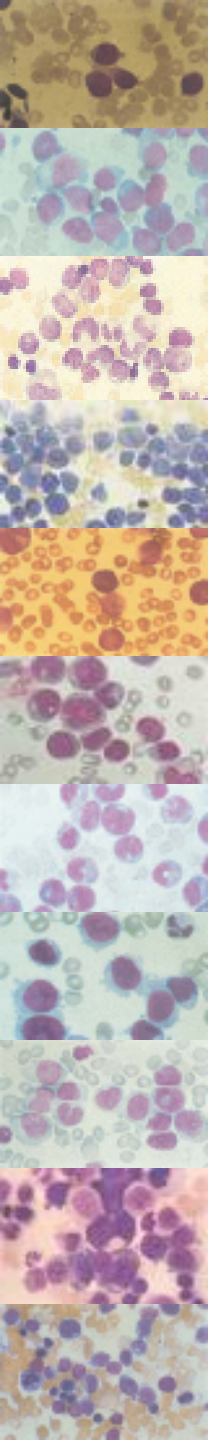


Oxaliplatin



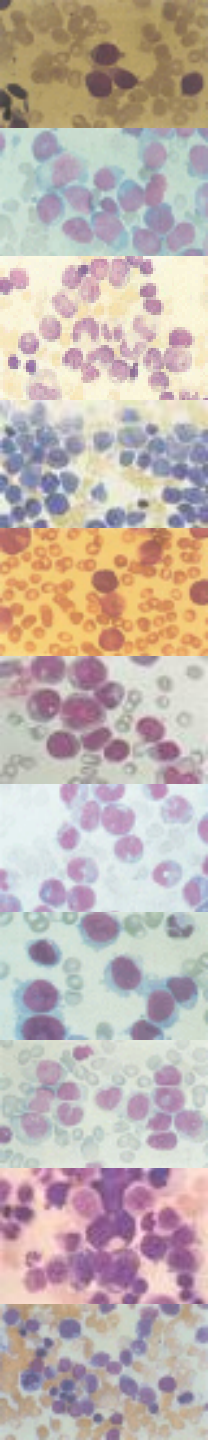
Cisplatin Toxicity

- **Hematologic toxicity**
  - can affect all 3 blood lineages
  - **minor** neutropenia, thrombocytopenia, and **ANEMIA**
  - its mild hematologic toxicity has allowed its combination with highly myelosuppressive chemotherapy
- **Ototoxicity**
  - audiograms show bilateral and symmetrical high frequency hearing loss
  - usually **irreversible**
  - caution with other drugs **(aminoglycosides)**



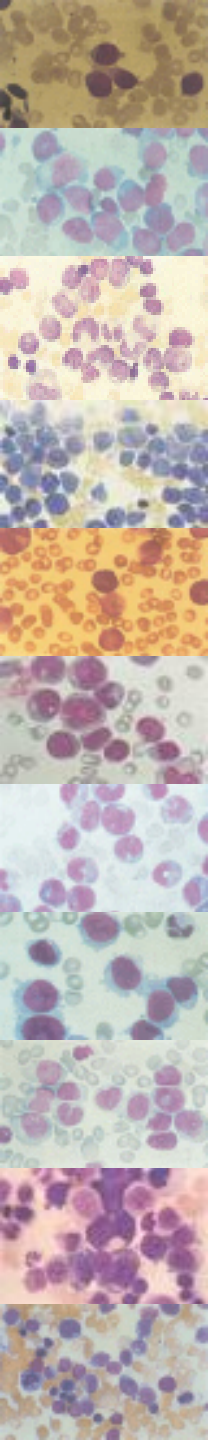
Cisplatin Toxicity

- **dose-limiting toxicity**
- most common symptoms are peripheral neuropathy and hearing loss
- less common include Lhermitte's sign (electric shock-like sensation transmitted down the spine upon neck flexion)
- autonomic neuropathy, seizures, encephalitic symptoms, and vestibular disturbances
- cumulative doses > 300 mg/m2
- first signs are loss of vibration sensation, loss of ankle jerks and painful paresthesias in hands and feet
- proximal progression and deficits in proprioception, light touch and pain
- recovery is typically incomplete



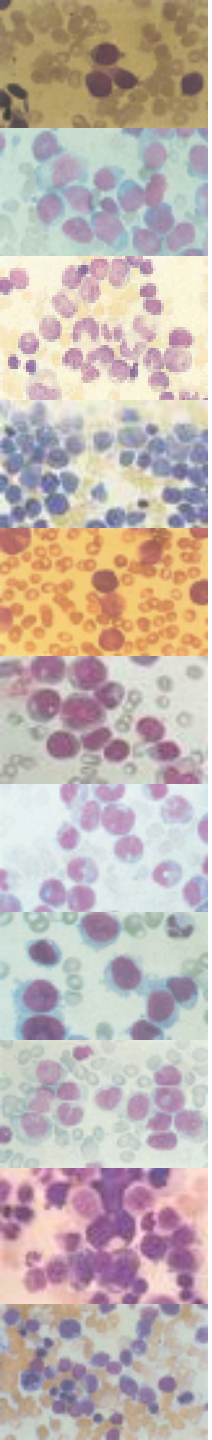
Cisplatin Toxicity

- **Nephrotoxicity**
  - dose-limiting toxicity
  - renal damage is usually reversible but rarely can be irreversible and require dialysis
  - platinum concentrations are higher in the kidney than in the plasma or other tissues
  - initiating event is proximal tubular lesion
  - secondary events such as disturbances in distal tubular reabsorption, renal vascular resistance, renal blood flow, and glomerular filtration, and polyuria seen 2 to 3 days later
  - hypomagnesemia develops in about 75% of patients, beginning 3 to 12 weeks after



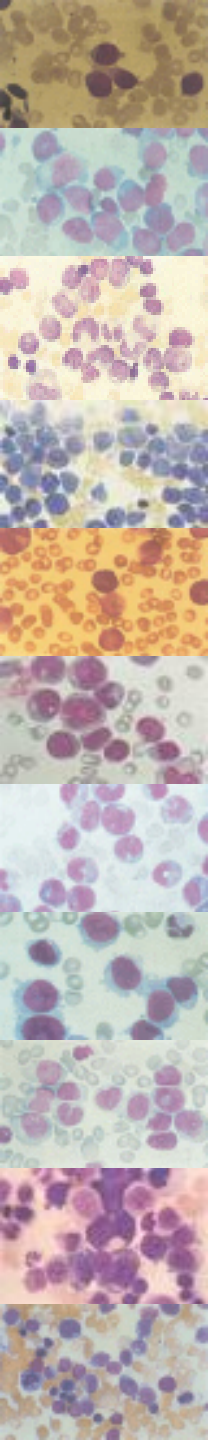
Cisplatin Nephrotoxicity

- **Preventive Measures**
  - aggressive saline hydration (enhance urinary excretion)
  - lower doses may require less hydration
  - infuse over 24 hours
  - pretreatment with amifostine
  - avoid other nephrotoxic agents
  - magnesium supplementation
  - predisposing factors to developing nephrotoxicity include age 60 years or older, higher doses, pretreatment GFR < 75 ml/min, cumulative dose, low albumin, single dose compared with daily x 5 administration schedules



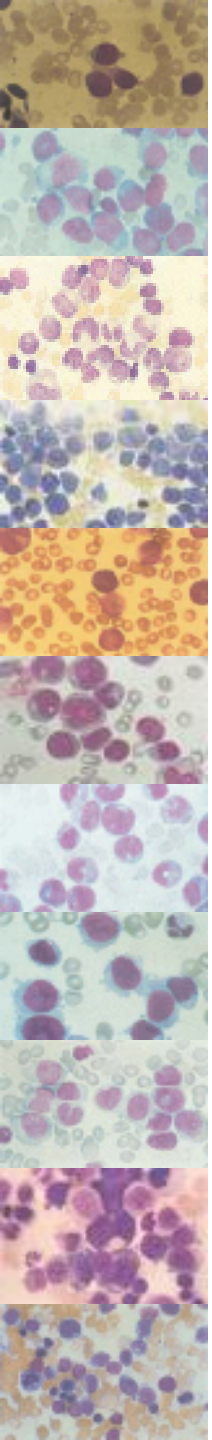
Cisplatin Toxicity

- **Nausea and vomiting**
  - acute or delayed
  - highly emetogenic if use doses $\geq$ than 50 mg/m^2
  - moderately emetogenic if use doses $\leq$ 50 mg/m2
  - **severe** if not adequately prevented with appropriate medications
  - **typical anti-emetic regimen**
    - aprepitant 125 mg po day 1 then 80 mg po days 2 – 3
    - dexamethasone 12 mg po day 1 then 8 mg po daily x 3 days
    - palonosetron 0.25 mg IVP day 1
    - metoclopramide



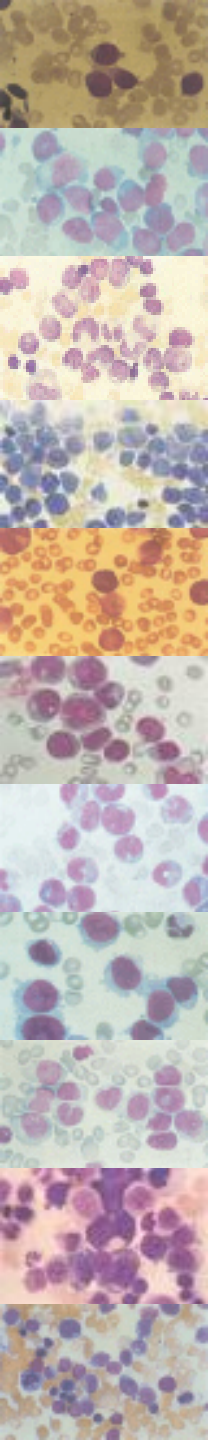
Carboplatin Toxicity

- **Moderately emetogenic**
- **Renal impairment is rare**
  - because it is excreted primarily in the kidneys as an unchanged drug, it is not directly toxic to the renal tubules
- **Neurotoxicity is rare**
- **Myelosuppression**
  - especially THROMBOCYTOPENIA
  - dose-limiting toxicity
  - cumulative
- **Hypersensitivity reaction**
  - thought to be due to type I hypersensitivity (IgE mediated)
  - incidence of hypersensitivity seems to be correlated with increased number of cycles of carboplatin administered
  - risk of hypersensitivity due to carboplatin exposure significantly increases during the sixth cycle, and it continues to increase up to cycle 8



Oxaliplatin Toxicity

- Gastrointestinal
  - Moderate emetogenicity
  - diarrhea
- Minimal hematologic toxicity
  - Thrombocytopenia is dose-related (doses > 135 mg/m2)
  - mild neutropenia
  - mild anemia
- No nephrotoxicity
- Hypersensitivity reaction
  - mild
  - generally subside upon discontinuation
  - slowing down infusion rate and giving an antihistamine and/or steroid
  - desensitization protocol
- Peripheral neuropathy
  - Prevention: Stop and Go Strategy, Ca and Mg infusions (may compromise efficacy



Clinical characteristics of oxaliplatin neurotoxicity

Acute symptoms

- Common (90% of patients)
- May appear at first treatment cycle
- Generally mild
- Onset during or within hours of infusion
- Transient, short lived
- Cold-triggered or cold-aggravated
- Dysesthesias and paresthesias
- Manifesting as stiffness of the hands or feet, inability to release grip, and sometimes affecting the legs or causing contractions of the jaw
- Distal extremeties, perioral, oral, and pharyngolaryngeal areas
- Depending on dosing schedule (infusion rate)

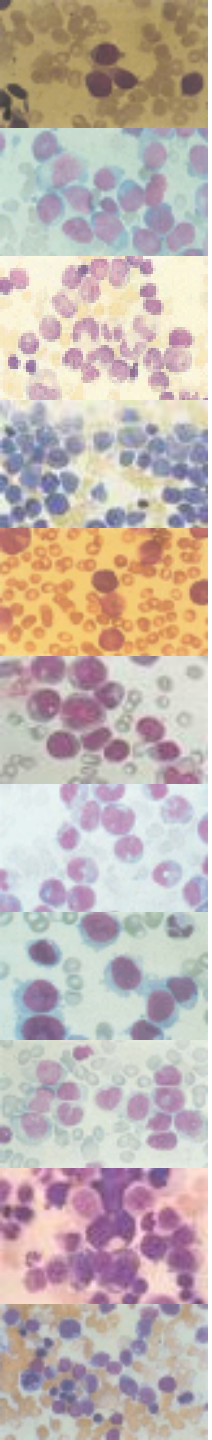
Chronic symptoms

- 10% to 15% moderate neuropathy after a cumulative dose of 780 to 850 mg/m^2
- Does not seem to be schedule-dependent
- Dysesthesias and paresthesias persisting between cycles
- Progressively evolving to functional impairment: difficulties in activities requiring fine sensorimotor coordination, sensory ataxia
- Tends to improve/recover after treatment is stopped
- Spares motor neurons (like cisplatin)

Comparison of Platinum Toxicity

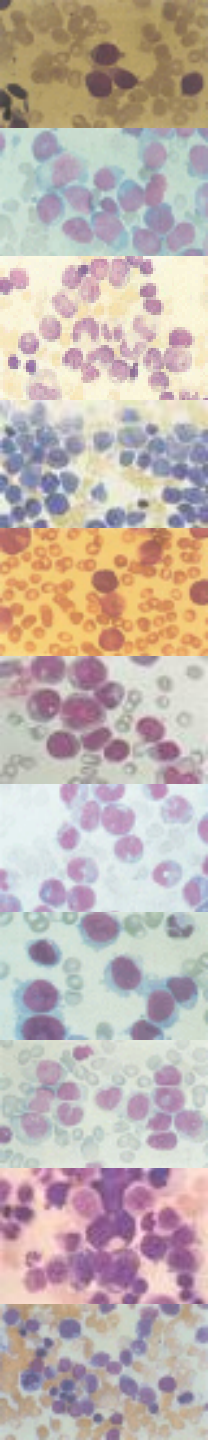
Table 5. Comparative adverse effect profiles of platinum drugs

Adverse effect	cisplatin	carboplatin	oxaliplatin
Nephrotoxicity	++	+	-
Gastrointestinal toxicity	+++	+	+
Peripheral neurotoxicity	+++	-	++
Ototoxicity	+	-	-
Hematologic toxicity	+	++	+
Hypersensitivity	-	+	-



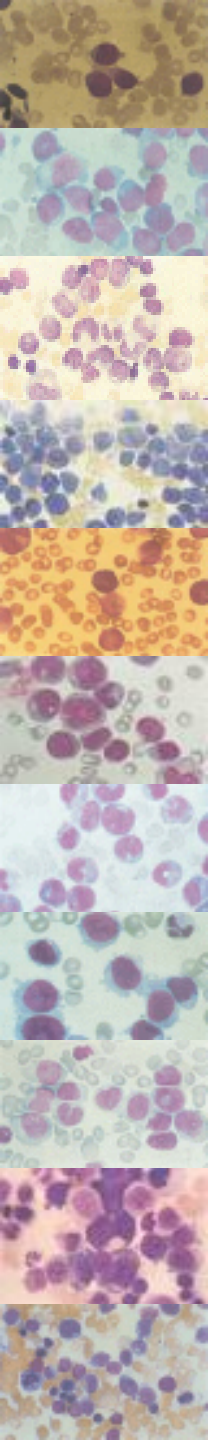
5-Fluoropyrimidines

- **History**
  - Rat hepatomas use uracil more efficiently than non-malignant tissue
  - 5-fluorouracil first introduced by Heidelberger et al in 1957
  - Capecitabine FDA-approved 4/30/1998
  - These are cell-cycle



Fluorouracil (5-FU)

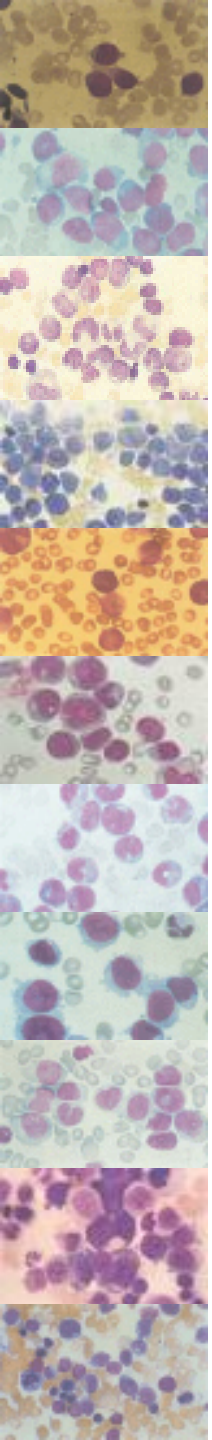
- **Mechanism of action**
  - 5-FU is a pro-drug, which is subject to both anabolism and catabolism
  - Cytotoxic activity of 5-FU depends on its anabolism to nucleotides, which exert their effects through inhibition of thymidylate synthase activity or incorporation into RNA and/or DNA
- **Chemical structure**
  - 5-fluoruracil is an analog of uracil with a fluorine atom substituted at the carbon-5 position of the pyrimidine ring in place of hydrogen
  - The deoxyribonucleoside derivative 5-fluoro-2'-deoxyuridine is commercially available (floxuridine, FUDR) and used primarily for regional administration (hepatic arterial infusion)



5-FU Toxicity

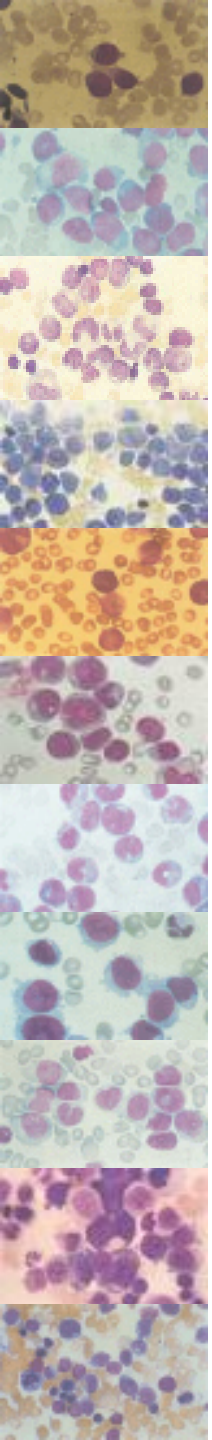
Toxicity is schedule dependent

- **bolus regimen (as in IFL)**
  - myelosuppression, oral mucositis, and gastrointestinal disturbances (diarrhea, nausea, vomiting, abdominal pain)
- **continuous infusion regimen (as in FOLFOX)**
  - hand-foot syndrome (dermal pain in hands and feet)
  - less hematologic



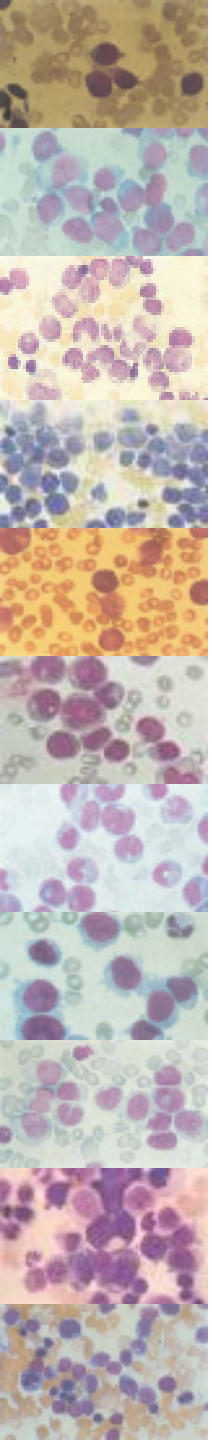
5-FU Toxicity

- **Cardiotoxicity** may be observed during treatment with 5-FU (2%-5% of cases), but symptoms disappear on stopping
  - The mechanism of toxicity is unknown but is proposed to be secondary to myocardial ischemia, potentially induced by **coronary vasospasm**
    - can rechallenge with nitrates
  - Patients most commonly present with chest pain during or after infusion that is angina-like in nature but may also experience cardiac arrhythmias, congestive heart failure, dilatative cardiomyopathy, cardiogenic shock, cardiac arrest, or sudden death syndrome



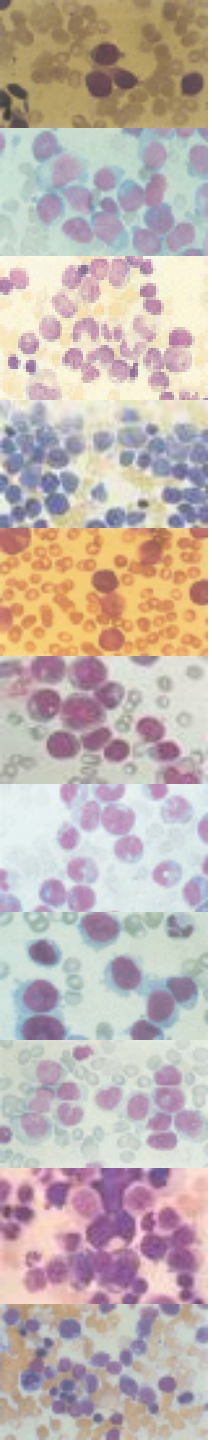
Other 5-FU Toxicities

- **Ocular Toxicity**
  - » Blepharitis, conjunctivitis, excessive lacrimation, ocular pruritus and burning
  - » This is due to tear duct stenosis
- **Hyperbilirubinemia**



Miscellaneous about 5-FU

- Low emetic potential
  - Give prochlorperazine 10 mg po 30 minutes before infusion UNLESS patient has history of previously uncontrolled N/V
- Not a vesicant or irritant
- Can cause serpentine veins (does not alter integrity of veins)
- hyperpigmentation over veins used for fluorouracil administration
- POTENT radiosensitizer
- Hepatic impairment: Need

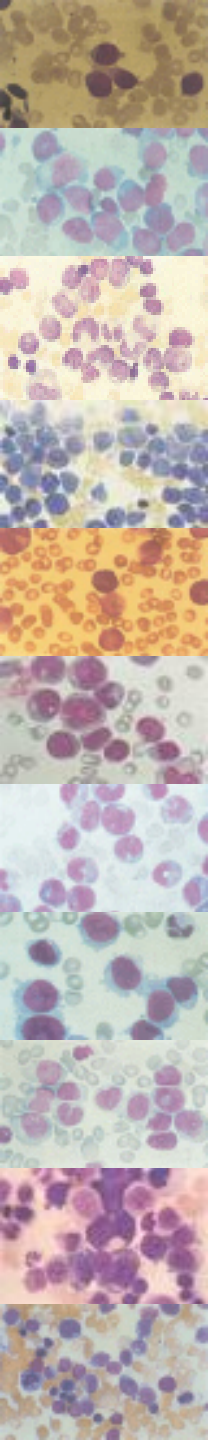


Capecitabine Toxicity

- Diarrhea, nausea/vomiting, abdominal pain, vertigo
  - low emetic potential: provide prochlorperazine prn N/V
- Hand-foot syndrome
  - Dose-limiting toxicity (mimics CI of 5-FU_
  - cutaneous adverse effect also referred to as palmar-plantar erythrodysesthesia or chemotherapy-induced acral erythema. The median time to onset is 79 days but can range from 11 to 360 days

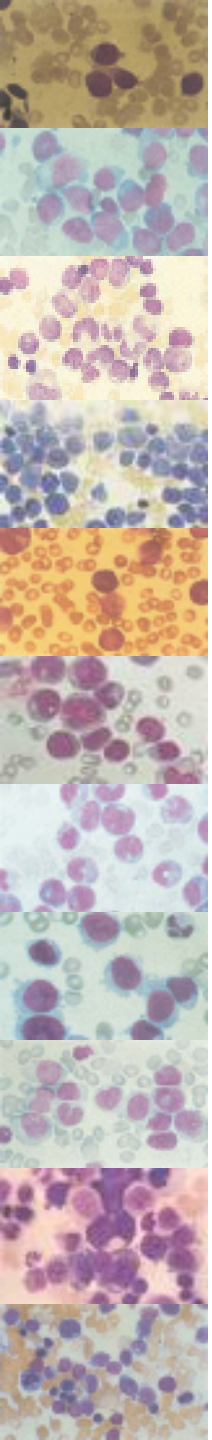
Capecitabine Hand-Foot Syndrome

- Supportive Care
  - Pyridoxine for prevention
  - Udderly® cream (moisturizer) to hands and feet
  - Avoid hot water because this can dry hands
  - Avoid tight clothing
  - Protect skin from sun (5-FU is photosensitizer and can cause 3rd degree burns if excessive sun exposure)
  - Wear gloves in winter or when going into freezer
  - Drug therapy mgmt: gabapentin, pregabalin



Capecitabine Warnings

- Concomitant administration with WARFARIN is a Black Box Warning
  - Bleeding events have occurred within several days to several months after initiation of capecitabine therapy and, in one case, several months after discontinuation of the drug
  - Time of onset of interaction is poorly differentiated and most likely due to individual variation in capecitabine metabolism
  - Elevated prothrombin time and/or bleeding event resulted in discontinuation of warfarin, capecitabine, or both
- Average time to reported elevated INR was 30.5 days (range 6–61), with an average INR of 12.4 (range 5.2–28.7)



Capecitabine Drug Interaction

- When given concomitantly with leucovorin, concentration of 5-FU is increased and toxicity is enhanced; deaths from severe enterocolitis, diarrhea, and diarrhea in elderly

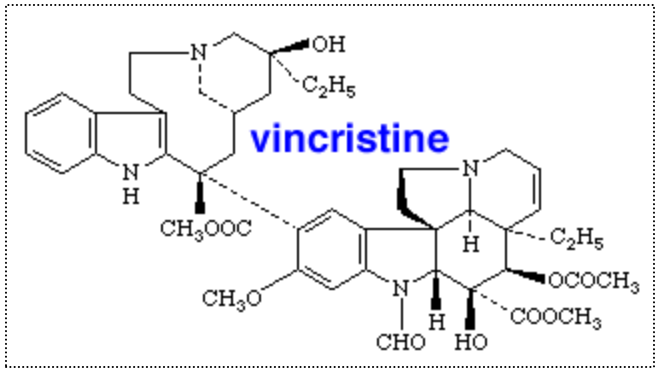
Table 1. Common Adverse Effects of 5-FU and Oral Fluoropyrimidines[a]

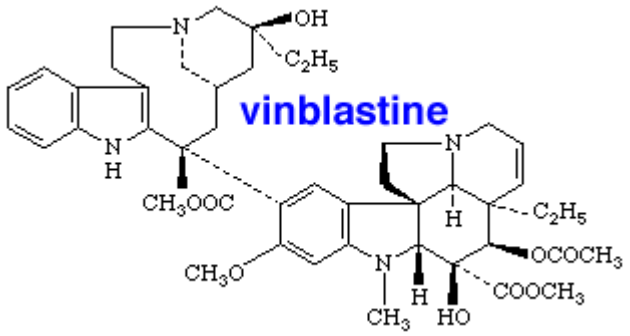
Adverse Effect	5-FU	Capecitabine	Eniluracil	UFT	S-1	BOF-A2
Diarrhea	X	X	X	X	X	X
Nausea/vomiting	X	X	X			X
Neutropenia	X		X		X	
Mucositis and stomatitis	X	X				
Hand–foot syndrome		X				
Anemia					X	

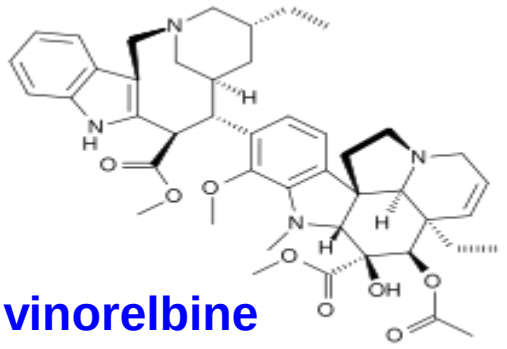
5-FU = fluorouracil; UFT = uracil + tegafur.
[a]Adapted from MacDonald[77] and Berg.[78]

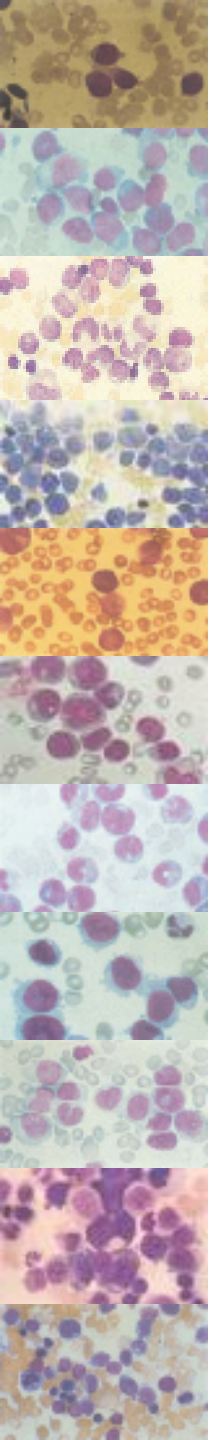
Vinca Alkaloids

The Vinca Alkaloids



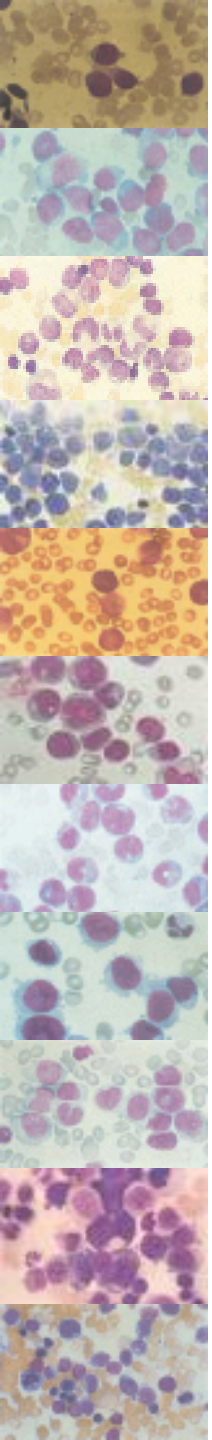






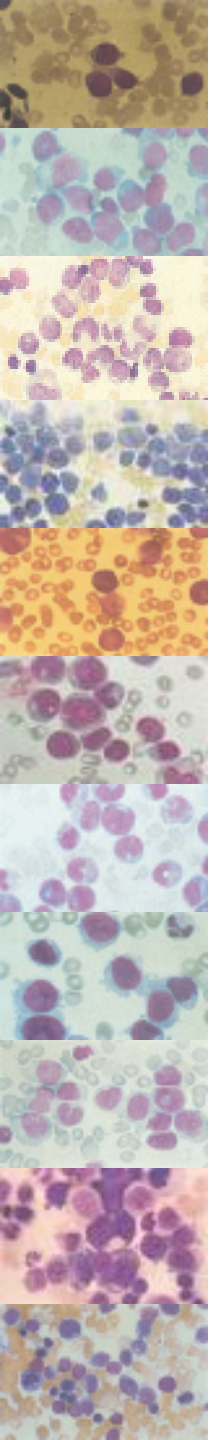
Vinca Alkaloids

- Mechanism of action
  - Bind to tubulin
  - Prevent polymerization of tubulin thus preventing microtubule formation
  - Chromosomes remain lined up in middle
  - Apoptosis
- Small differences in structure changes toxicity and activity
  - vincristine active in leukemia and is neurotoxic
  - vinblastine active in lymphomas and testicular cancer and is myelosuppressive
  - vinorelbine active in lung cancer and is neurotoxic and myelosuppressive



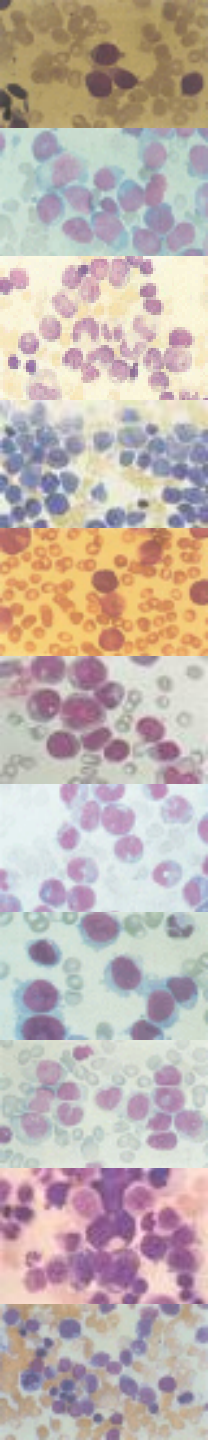
Vincristine Toxicity

- Neuropathy
  - dose limiting
- Initially symmetrical sensory impairment
  - Parasthesias in distal extremities – cumulative
  - Neuropathic pains
  - May be reversible
- Motor nerve impairment with continued use
  - Loss of deep tendon reflexes
  - Ataxia
  - Foot and wrist drop, paralysis
  - Irreversible or minimally reversible
- Severe toxicity if given to someone with pre-existing neurological disorders



Vincristine Toxicity

- Demyelination of nerve fibers
- Unmyelinated nerves most sensitive – DTRs
- Cranial nerves with continued use
  - hoarseness, Diplopia, Facial palsy
  - jaw, parotid and pharyngeal pains
- CNS toxicity
  - depression, confusion, agitation, hallucinations and seizures, hearing loss
- Autonomic: Constipation, paralytic ileus
- SIADH

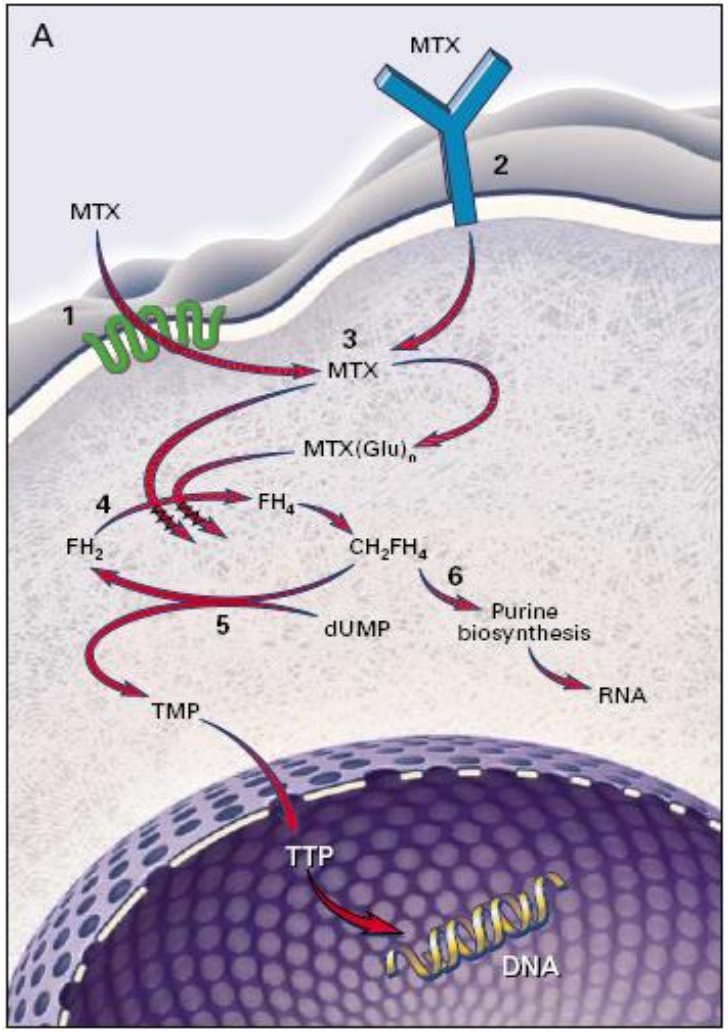


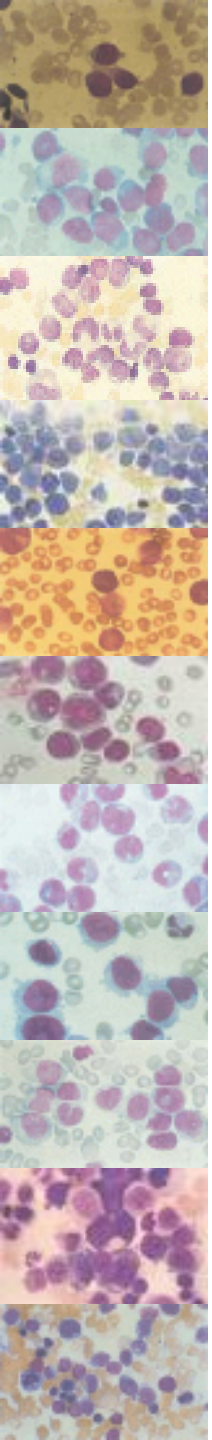
Vincristine Toxicity

- Cardiac autonomic dysfunction
  - Orthostatic hypotension, hypertension
- GI
  - Constipation
  - Not very emetogenic
- GU
  - Bladder atony – incontinence, dysuria, urinary retention
  - Avoid anticholinergics if possible
- Dermatologic: Vesicant
  - Local heat, hyaluronidase, corticosteroids

Methotrexate

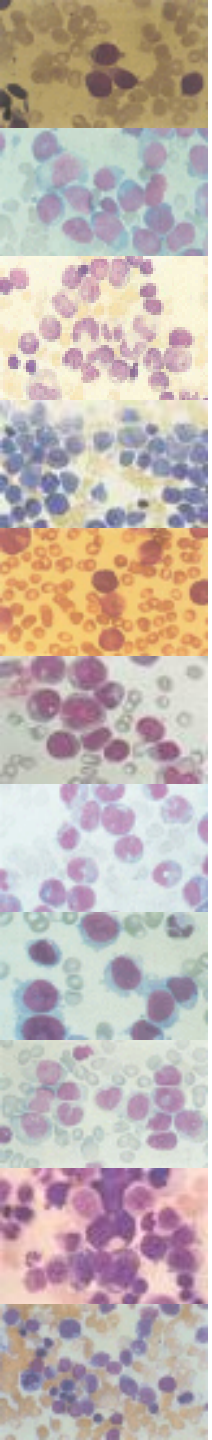
- **Mechanism of action**
  - Folic acid analog
  - Cell cycle specific (S-phase)
  - Inhibits dihydrofolate reductase, depleting intracellular pools of tetrahydrofolate which is essential for purine and thymidylate synthesis (DNA synthesis)
- **Pharmacology**
  - MTX becomes polyglutamated once inside the cell
  - Cytotoxicity is concentration and time dependent





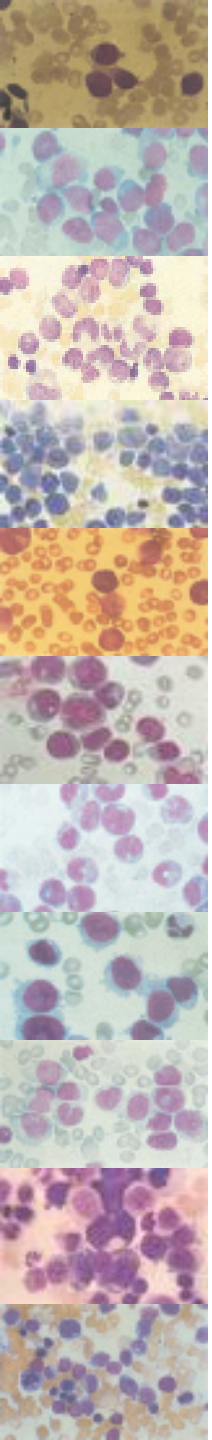
Methotrexate

- **Pharmacokinetics**
  - Distributes widely in body tissues and total body water
    - Caution in patients with pleural effusion, ascites, 3rd spacing)
  - Low CNS penetration with conventional doses
  - Renal elimination
    - Filtered and actively secreted
    - Clearance approximates creatinine clearance
    - At higher doses, concentrations in renal tubules may exceed MTX urine solubility and cause renal damage from crystallization
- **Doses**
  - Low dose: < 1 gram/m^2
  - High dose: 1 – 30 gram/m^2
  - Intrathecal: usually flat dosing (12 or 15 mg)



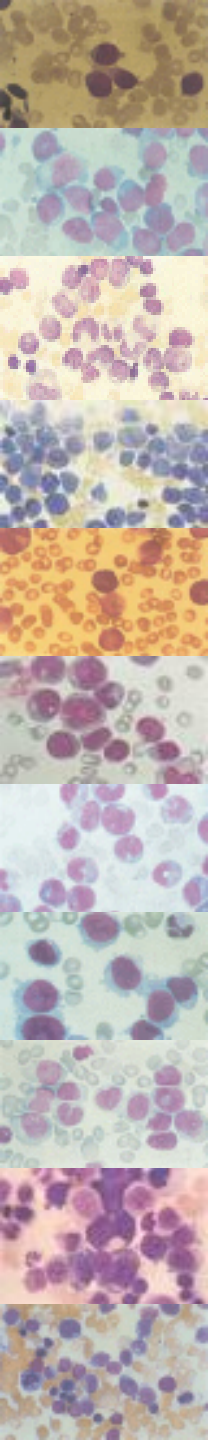
High-Dose MTX

- Patient must have adequate **marrow, liver, and renal** function before therapy
- Maintain **UOP > 100 ml/hr**
- Maintain **urine pH > 7**
  - Add sodium bicarbonate or acetate to IVF
  - Give oral sodium bicarbonate or oral acetazolamide
- **Principle of high-dose MTX**
  - At high plasma levels, passive entry into tumor cells can overcome resistance due to defective active transport
  - Increased free intracellular MTX levels can overcome resistance secondary to increased DHFR or altered enzyme binding
  - High, prolonged plasma levels increase polyglutamate formation and prolongs drug action



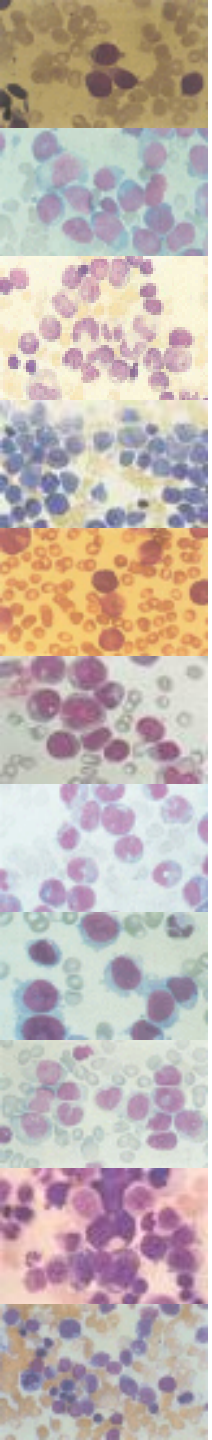
Leucovorin

- **Mechanism of action**
  - Derivative of FH_4
  - Competes with MTX for active transport into cells
  - Enters folate cycle distal to MTX enzymatic block
  - Given AFTER MTX as “rescue” by repleting intracellular FH_4 pools
  - Selective for rescuing normal cells more than malignant cells
  - May compromise antitumor efficacy if given early
- **Administration**
  - Started 24 hours after MTX
  - After 48 hours, MTX toxicity may not be reversible with leucovorin
  - Continue until MTX levels < 0.05 μM
  - 1:1 IV: po (100% bioavailability)



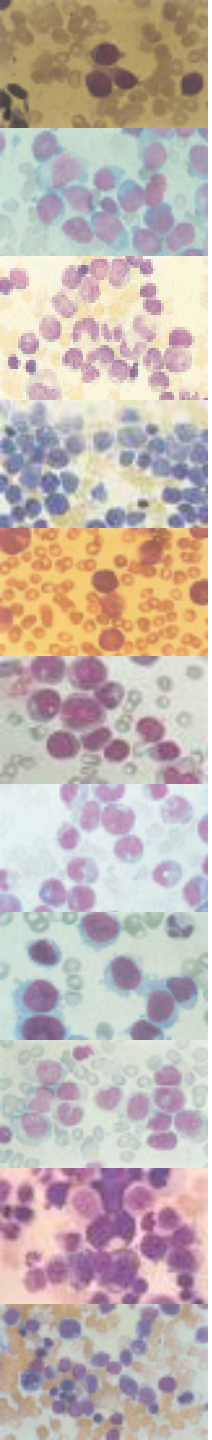
MTX Toxicity

- **Schedule and dose dependent**
- **Myelosuppression**
  - Nadir is 10 days and recovery usually within 14 to 21 days
- **Mucositis**
  - 3 to 5 days after treatment
  - Can be life threatening, requiring dose interruption
- Diarrhea
- **Nausea and vomiting (dose dependent)**



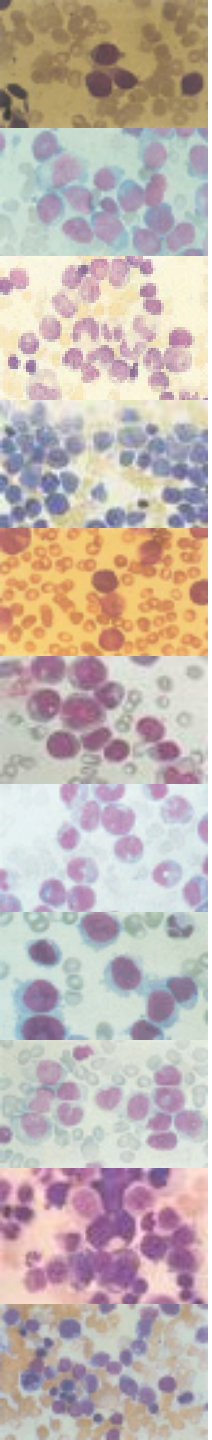
MTX Toxicity

- **Renal**
  - Direct cytotoxicity on tubular cells or precipitation
  - pKa of MTX is 5.4 (insoluble in acidic urine)
  - Precipitation of MTX and 7-OH metabolite
  - Alkalanize urine (pH > 7)
  - Vigorous hydration (UOP > 100 ml/hr)
  - Requires dosing adjustment in renal insufficiency
- **Hepatic**
  - Fibrosis, cirrhosis more common with chronic, low dose oral therapy
  - Pulse dosing decreases risk
  - With HD MTX, transient increases in transaminases within 24 hours
  - Requires dosing adjustment in hepatic insufficiency



MTX Toxicity

- **Pulmonary**
  - Less common, but potentially fatal
  - Fever, dry cough, dyspnea, chest pain
  - Responsive to corticosteroids
- **Neurotoxicity (IT therapy)**
  - Arachnoiditis: headache, nuchal rigidity, fever, vomiting - common, acute in onset
  - Motor paralysis, nerve palsy, seizures, coma during 2nd or 3rd week of treatment, typically in patients with meningeal leukemia
  - Chronic demyelinating encephalopathy with dementia, spasticity, coma – can occur months to years after treatment (irreversible); XRT followed by MTX can cause leukoencephalopathy
- **Other: rash, HSV, teratogenicity, alopecia**



MTX Drug Interactions

- **Avoid concomitant nephrotoxins**
  - Cisplatin, probenecid, NSAIDS compete for excretion and decrease elimination of MTX
- Salicylates and sulfonamides (Bactrim, PCN) may displace MTX from binding sites
- Oral antibiotics may interfere with oral absorption of MTX and with enterohepatic recycling

GRACIAS