Principles of Chemotherapy

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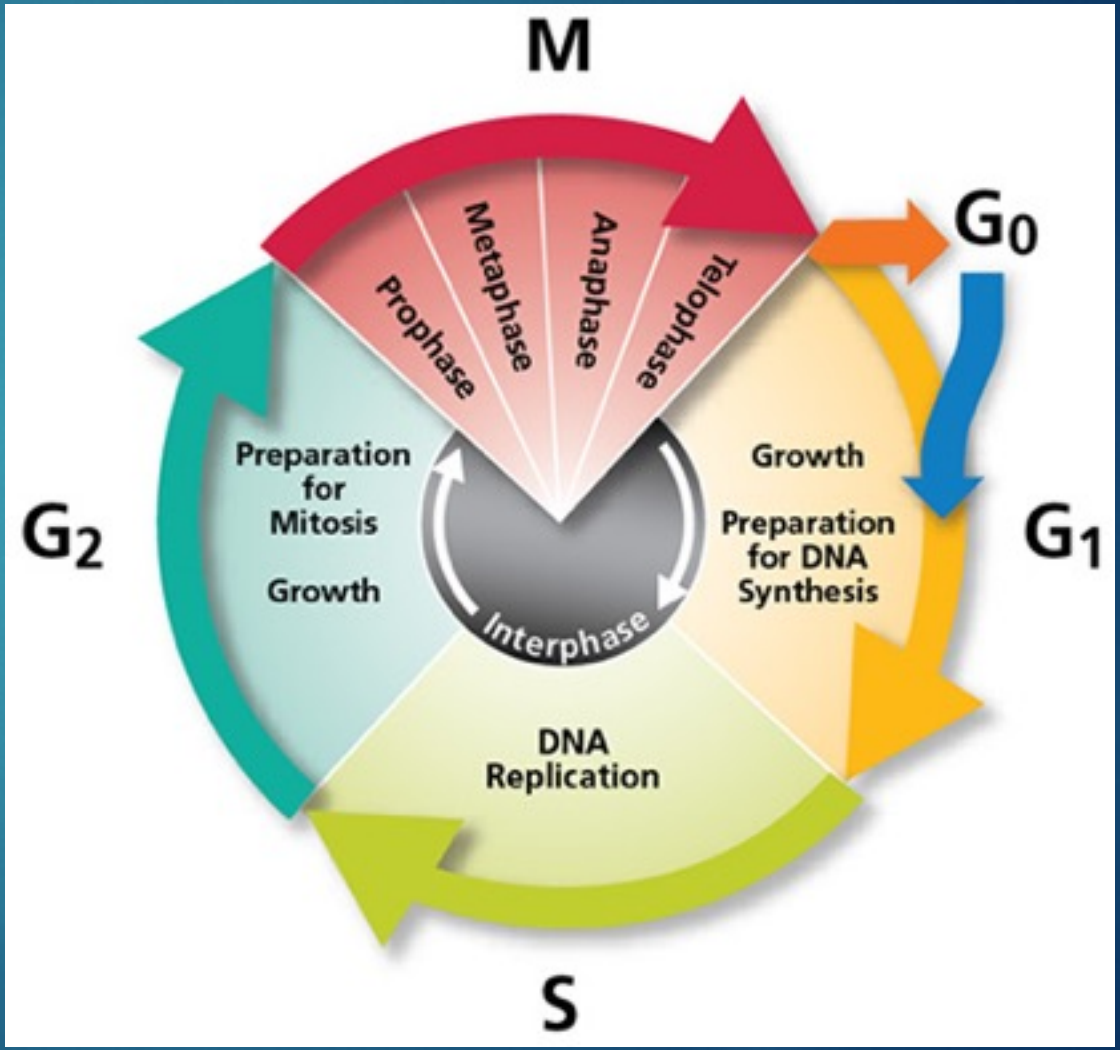
Biology 101

- Cancer is a complex disease caused by genetic and epigenetic mutations
  - Simply, it is only unregulated cell division
- "Traditional" chemotherapy highjacks mechanisms of mitosis
- Understanding chemotherapy needs understanding of Biology 101*



* Of course it gets complicated

Chemotherapy

- Merriam-Webster: Chemotherapy: *noun*: che · mo · ther · a · py
  - Medical: The use of chemical agents in the treatment or control of disease (such as cancer) or mental illness
- Word originated around 1910 by Paul Ehrlich
  - Developed the first treatment for syphilis, antiserum for diphtheria (Nobel prize in 1908)
  - He also developed the concept of "magic bullet"
- In the world of pharmacology chemotherapy can be used to treat:
  - Infectious disease
  - Cancer

History of Chemotherapy Begins…

World War II

- Nitrogen Mustards were taboo and not used in battle, however
  - Ready to be used (and feared that Hitler would use them when he was pushed)
- Bomb raid on Bari, Italy on December 2nd, 1943
  - Sailors exposed were noted to have depletion of bone marrow stores and depleted lymph nodes
- Goodman and Gilman at Yale discovered murine models with lymphomas responded to nitrogen mustard therapy
  - Convinced a surgeon to treat a single NHL patient with a nitrogen mustard
  - Original trial done in 1943, but data kept secret until 1946

The Lesson of the 1940s

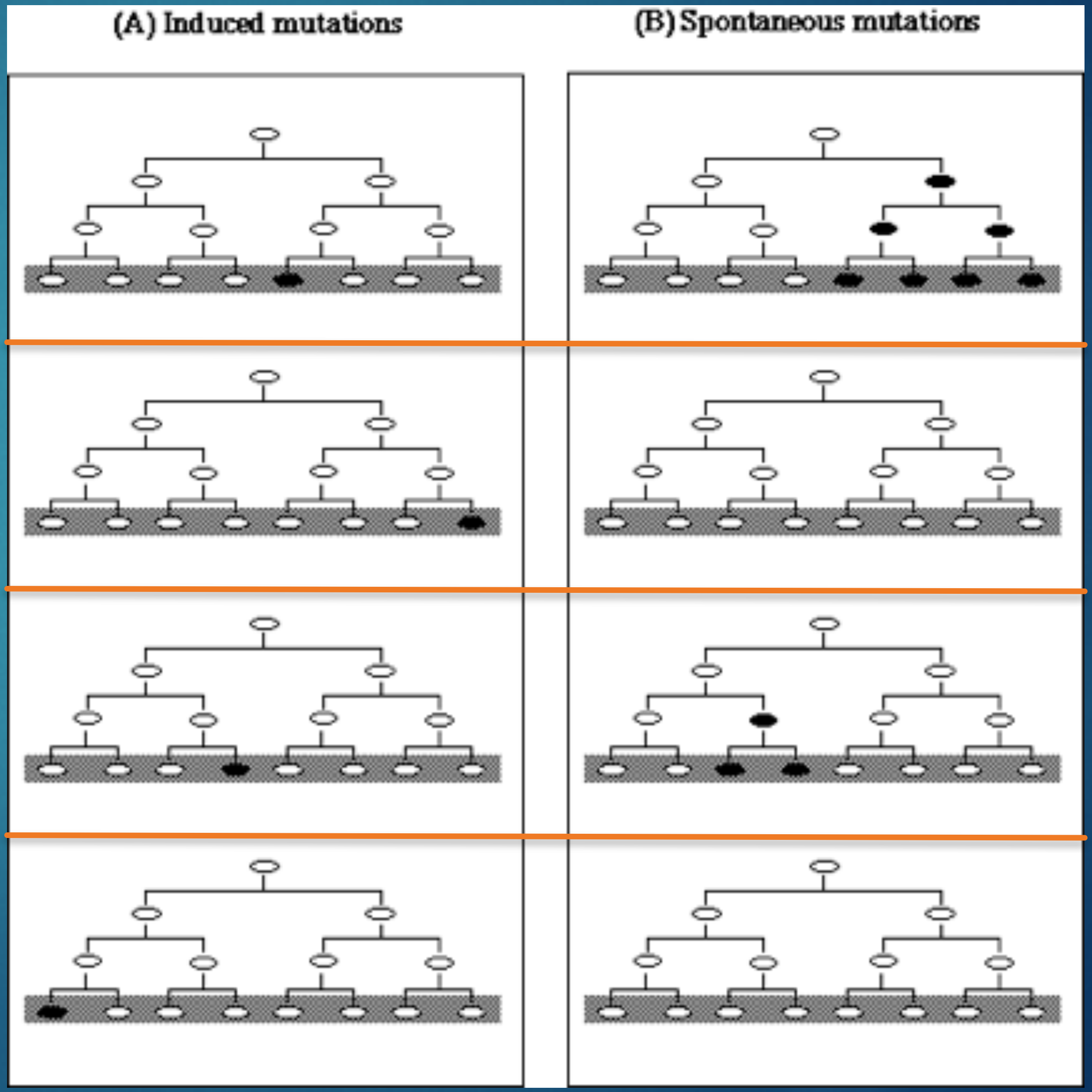
- Nitrogen Mustards: Alkylation of guanine nucleotides in DNA causing inhibition of cell division and ultimately apoptosis
- Showed promise however, responses to therapy was short in duration and ultimately relapsed
- 1949: Sidney Farber (Dana-Farber), born in Buffalo, NY discovered folic acid accelerated childhood leukemia growth
  - Antifolates (aminopterin) induced significant remissions in pediatric leukemias
    - Short lived, and relapsed
- So what contributed to failure?

Luria and Delbruck

- Go back to bacteria and how mutations arise?
- Took two groups of plates of bacteria and exposed them to a virus for infection
  - If resistance to the virus were due to exposure, then there would be the same number of resistant colonies
- Turns out the number of resistant colonies varied significantly between plates
- Resistance is due random mutations
- Cancer cells are no different from this:
  - Some are inherently resistant to a chemotherapy agent due to randomness alone

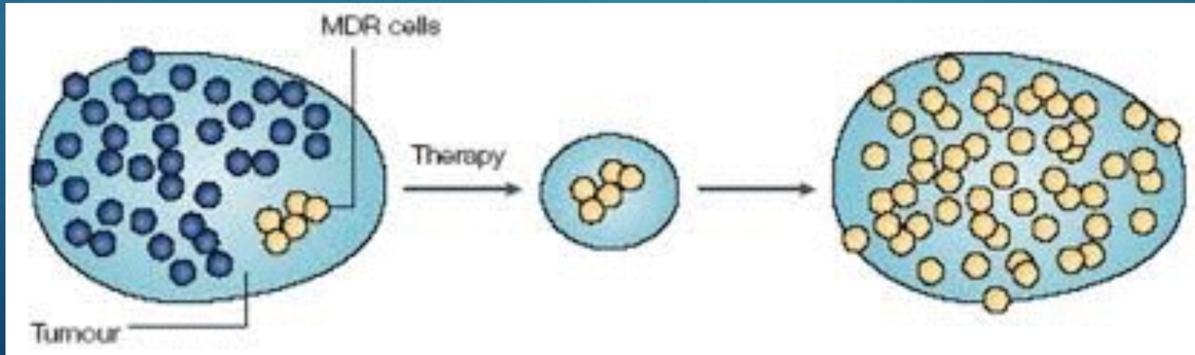
Luria and Delbruck

- Column A represents cultures where natural selection would look
  - Darwinism
- Column B is randomness
- Column B explains why chemotherapy is inherently resistant to single agent chemotherapy



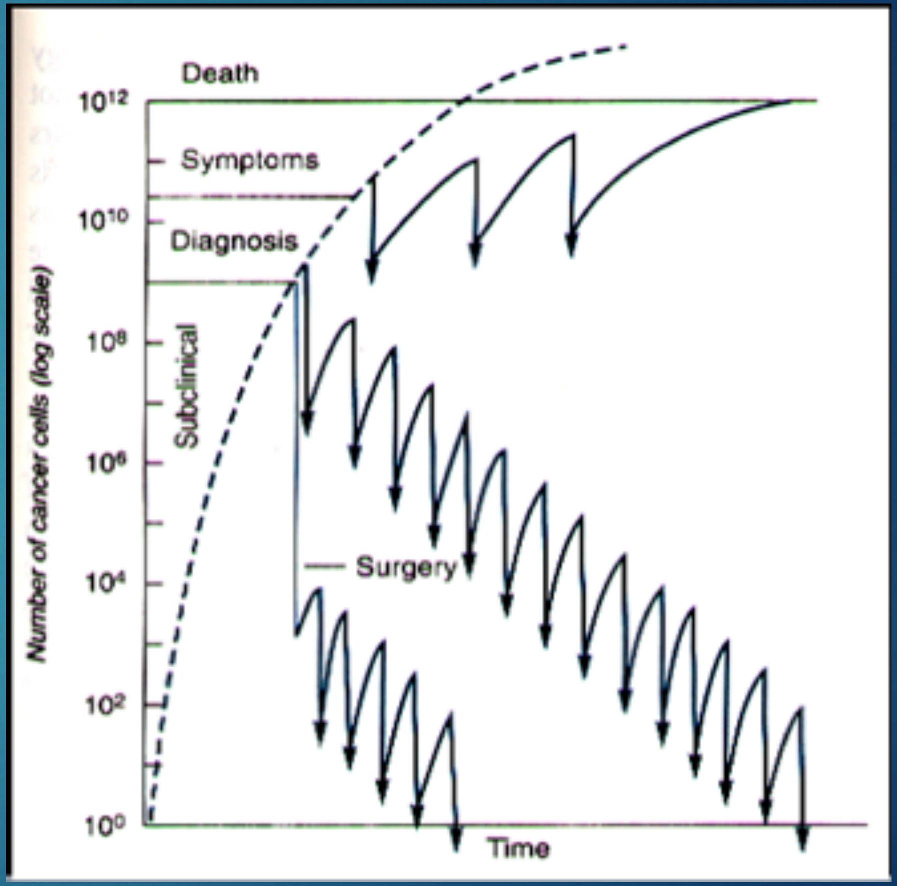
Goldie – Coldman Hypothesis

- Mathematical Model predicts the likelihood of developing somatic mutations that lead to drug resistance
  - Probability of resistance to a drug is greater as the size of a tumor increases and/or the rate of division increases
  - Usually this develops even before the cancer is clinically detectable
- Cancer is best treated by concomitant chemotherapeutic regimens (multiple drugs given at the same time)
- Principles taken so far:
  - Tumors need to show sensitivity to each agent as a single agent
  - Drugs used in combination should have different mechanisms of action



Cancer Growth and Dynamics

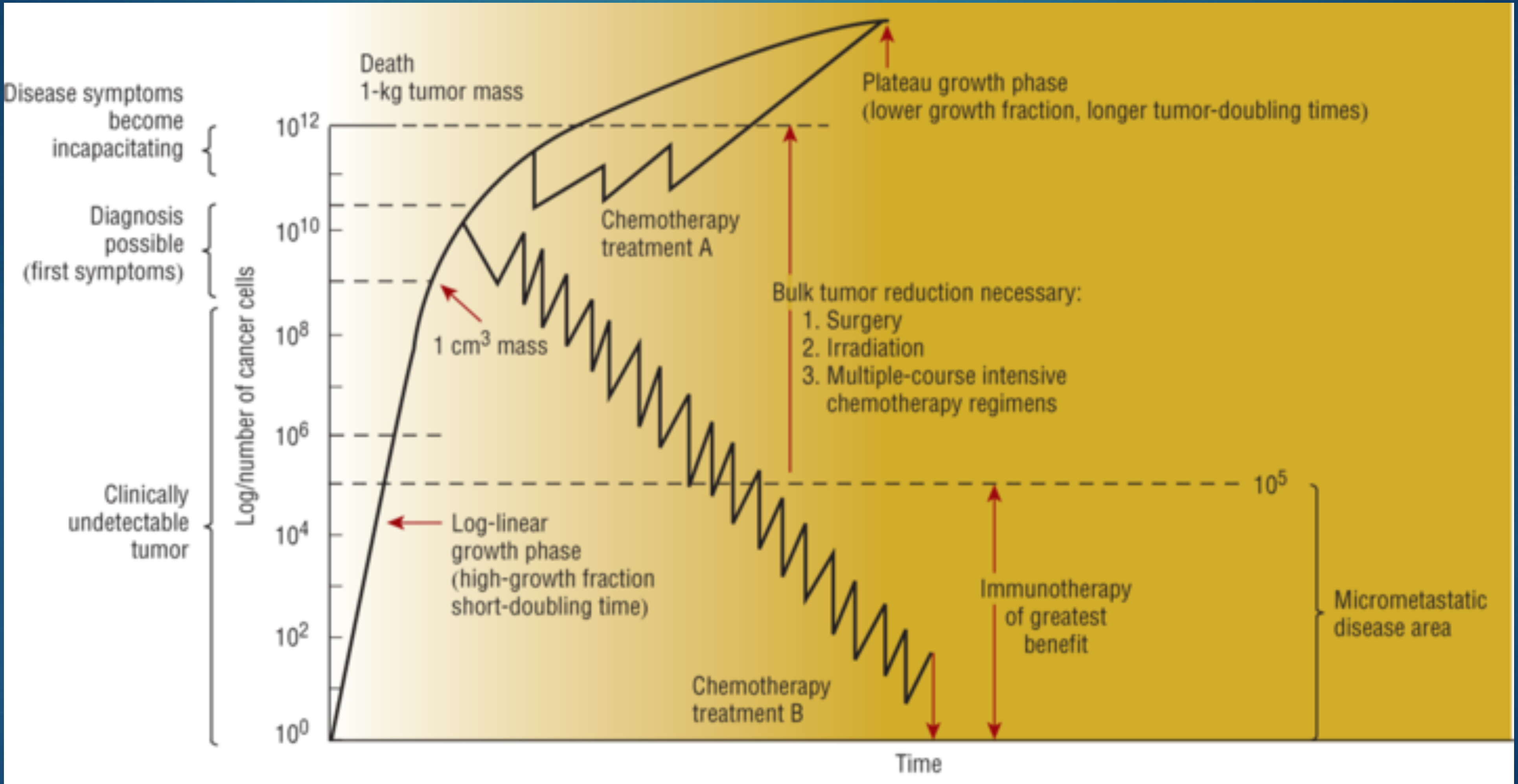
- Gompertzian growth
- Fraction of tumors progressing thru cell cycle influences susceptibility
  - AKA growth fraction
- 10^9 Cells!!! Clinical Symptoms
- As time increases:
  - Cells develop resistance inherently
  - Competition over nutrients
  - Less cells going through division
- Other fast growing cells:
  - GI/buccal mucosa
  - Hair follicles
  - Bone marrow



Types of Chemotherapy Regimens

- Adjuvant chemotherapy
  - Chemotherapy given after surgery
  - Goal is to eradicate micrometastasis and decrease recurrence
- Neoadjuvant chemotherapy
  - Chemotherapy given before surgery
  - Goal is to shrink the tumor for resection
- Palliative chemotherapy
  - Improve symptoms/ QOL
  - "Gentler" in nature
- Curative chemotherapy
  - More aggressive treatment
  - Traditionally associated with more toxicities

Cancer Growth and Regimens



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach, Ninth Edition*: www.accesspharmacy.com

Fractional Kill Hypothesis

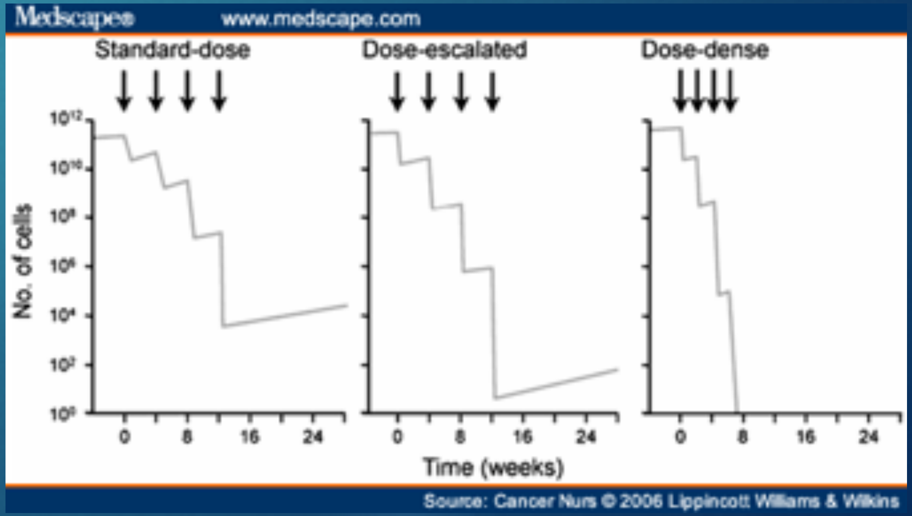
- Also called “log-kill hypothesis”
- Assuming homogenous sensitivity to a drug, drugs will act on first order kinetics
  - They will eliminate a constant *proportion* of cells rather than a constant *number*
  - Cell kill is a logarithmic function
- Explains that multiple doses need to be given
- Partially explained by drugs only effecting specific steps in the cycle
  - Leukemic S-phase ~ 18 – 20 hours, cytarabine given Q12H
- Establishes the role of adjuvant therapy to treat micrometastatic disease or small volume disease
- Higher doses may give a larger proportion of cells killed

Norton – Simon Hypothesis

- "Chemotherapy results in a rate of regression in tumor volume that is proportional to the rate of growth for an unperturbed tumor of that size,"
  - Log – kill does not work in all situations, especially solid tumors
  - Not all cells are rapidly dividing, high growth fraction
- In other words, tumors are heterogeneous in nature
  - Some are faster-growing, others are slower growing
- Tumors are best eradicated by more frequent, lowest effective dose chemotherapy regimens

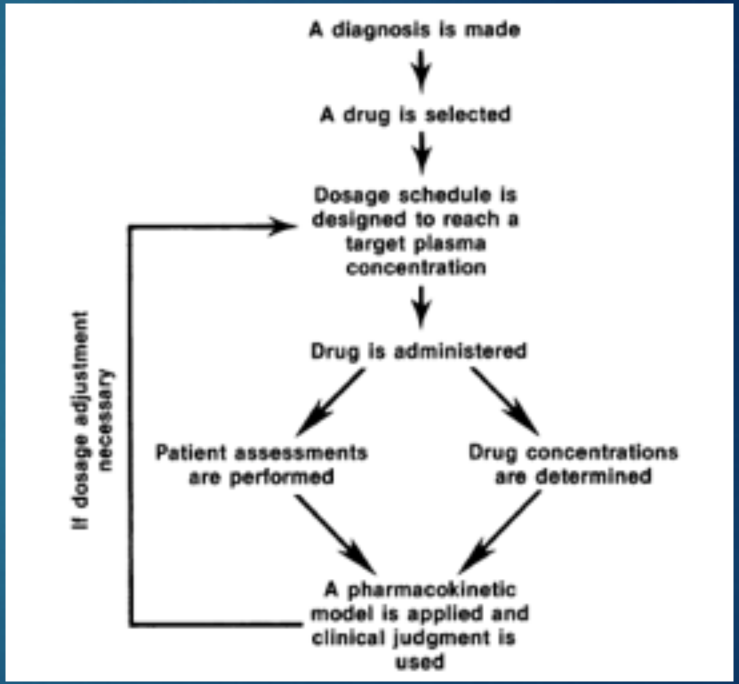
Dose Intensity vs Density

- The best scenario: highest dose of chemotherapy with the shortest interval possible
- Dose intensity (escalation): variable dose over a fixed unit of time
  - 90 mg/m^2 for 3 days vs 60 mg/m^2 for 3 days of etoposide
  - Subject to side effects
  - Analogous to concentration – dependent antibiotics
- Dose density: fixed dosed over a variable unit of time
  - AC (DD) regimen given every 14 days vs 21 days
  - Analogous to time – dependent antibiotics



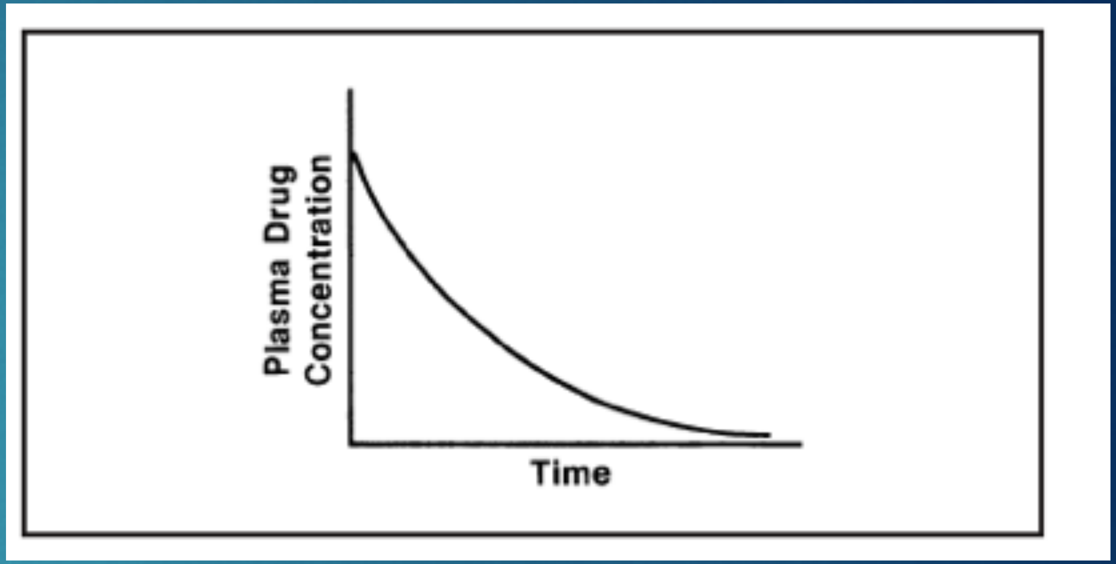
Pharmacologic Properties of Drugs

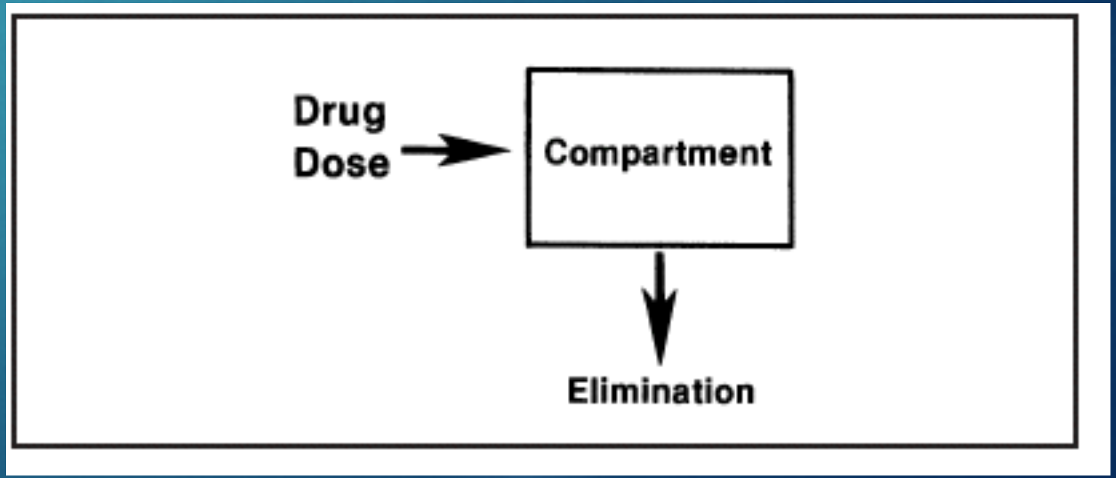
- Why do so many promising drugs fail therapy once they go into humans?
  - Movement from petri dishes to humans is a big jump
- Pharmacokinetics: Study of drug pathway through the body
  - A: Absorption
  - D: Distribution
  - M: Metabolism
  - E: Elimination
- Pharmacodynamics: Study of the concentration of drug at the site of the effect
- Pharmacogenomics: Relationship with genomic variation on the individual on the kinetics and dynamics of the drug



Pharmacokinetics: The Basics

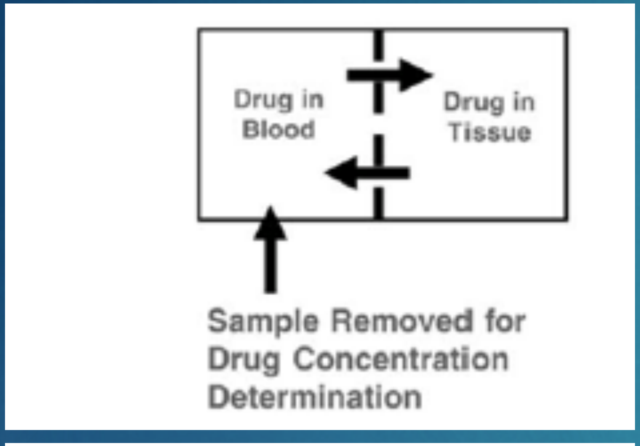
- Simple, IV bolus one-compartment model:
  - A: none. Bypassed when given IV
    - Otherwise drug levels would go up before they go down
  - D: none. Contained in one compartment (vasculature)
  - M: none
  - E: Constant
- Body Systems are far more complicated then this

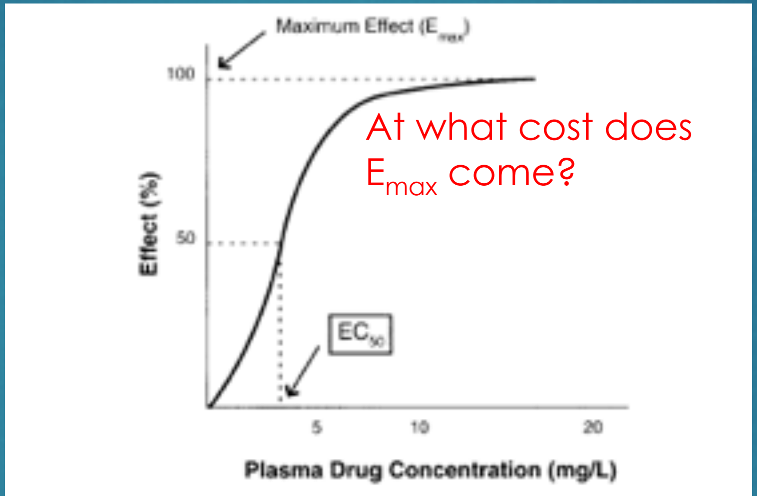


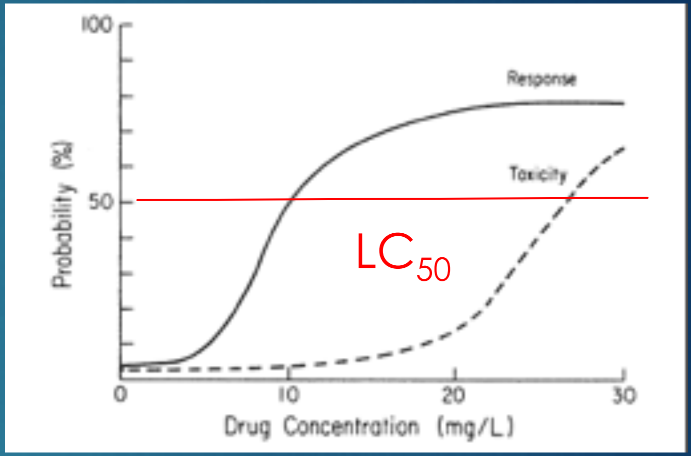


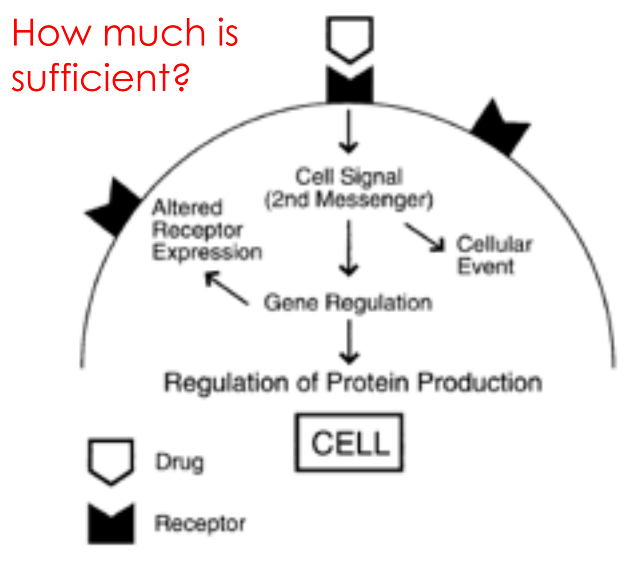
Pharmacodynamics

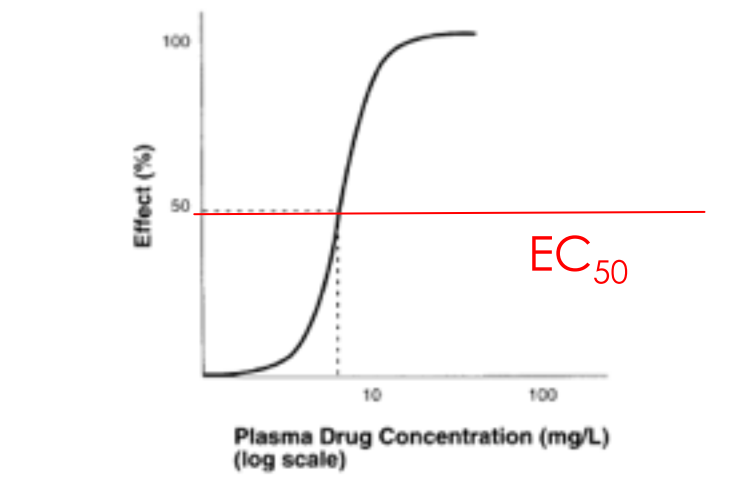
- Assuming that concentration of blood has a relationship to that in tissue, establishes potency:

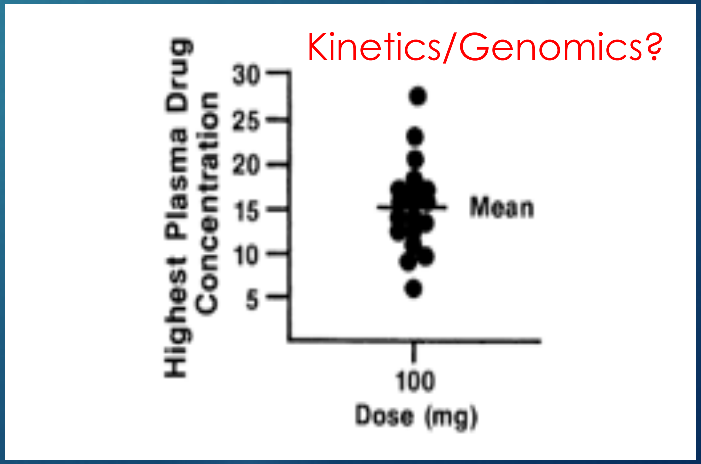




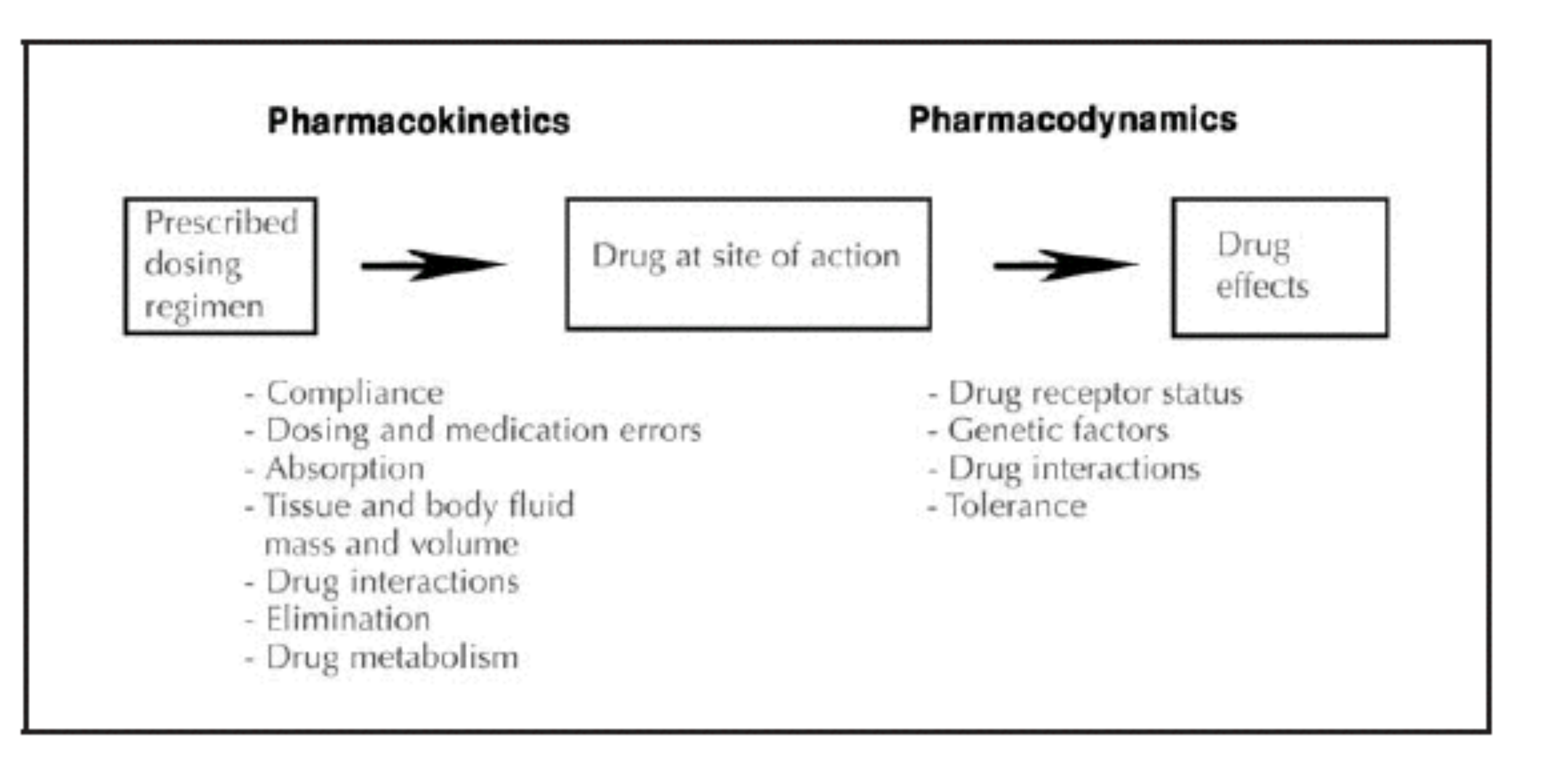








Drug Pathway Through The Body



- Highlights the overall complexity of the relationship of drug, effects and toxicities
- Mastering these with OPTIMIZE the effect of the drug while limiting toxicity

How is Dose Calculated?

- Fixed Dose: Dose is the same regardless of patient specific factors
  - Example: Pertuzumab (Perjeta) 840 mg IV x1, then 420 mg thereafter
- Age Based Dosing
  - Example: Dosing of chemotherapy in infants
- Weight Based Dosing: Dosing based on body weight in kg (TBW/IBW/ABW?)
  - Example: Bevacizumab 5 mg/kg IV every 2 weeks
- Body Surface Area: Most common
  - $\sqrt{\frac{weight\ (kg) \times height\ (in)}{3600}}$
  - Cisplatin 75 mg/m^2 IV every 3 weeks
- Others:
  - Calavert Equation for Carboplatin: Based on AUC and renal function

Eastern Cooperative Oncology Group (ECOG) Performance Status

- Assuming an equivalent BSA and same type/stage of cancer, is a 30 year old athlete going to tolerate the same therapy the same as a 70 year old chronic smoker on dialysis who cannot work?
- ECOG Performance Status (PS)
  - Standard to measure the impact of disease on daily living
  - Used extensively in clinical trials
- Changes of PS are one reason why doses and therapies change
  - Consider changes in PK/PD
- 70 year patient might start with lower dose or different therapy all together

Table 1. ECOG Performance Status categories

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
5	Dead

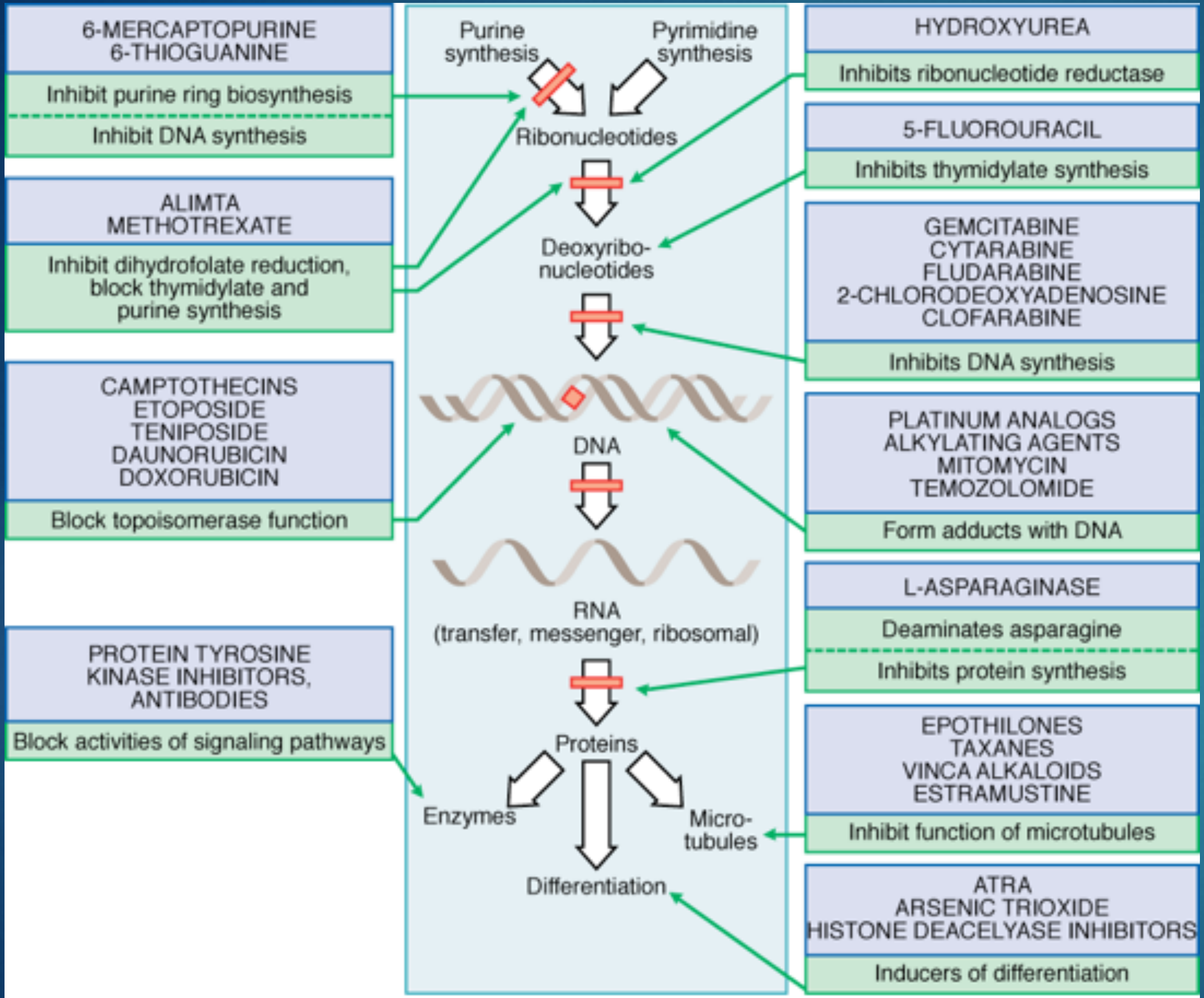
Adapted from Oken, et al.1982
ECOG = Eastern Cooperative Oncology Group

Review of Principles…

- The tales of the 1940's taught that disruption of cell cycle can effect cancer growth
- Combination of agents may help prevent resistance and improve outcomes
- Cancer cell growth is not constant
- Chemotherapy can be given at different doses, frequencies and in combination with other modalities
- How the drug reacts in Petri dish is different from in the body
- Chemotherapy is toxic
- Chemotherapy is tailored to the patient and the cancer

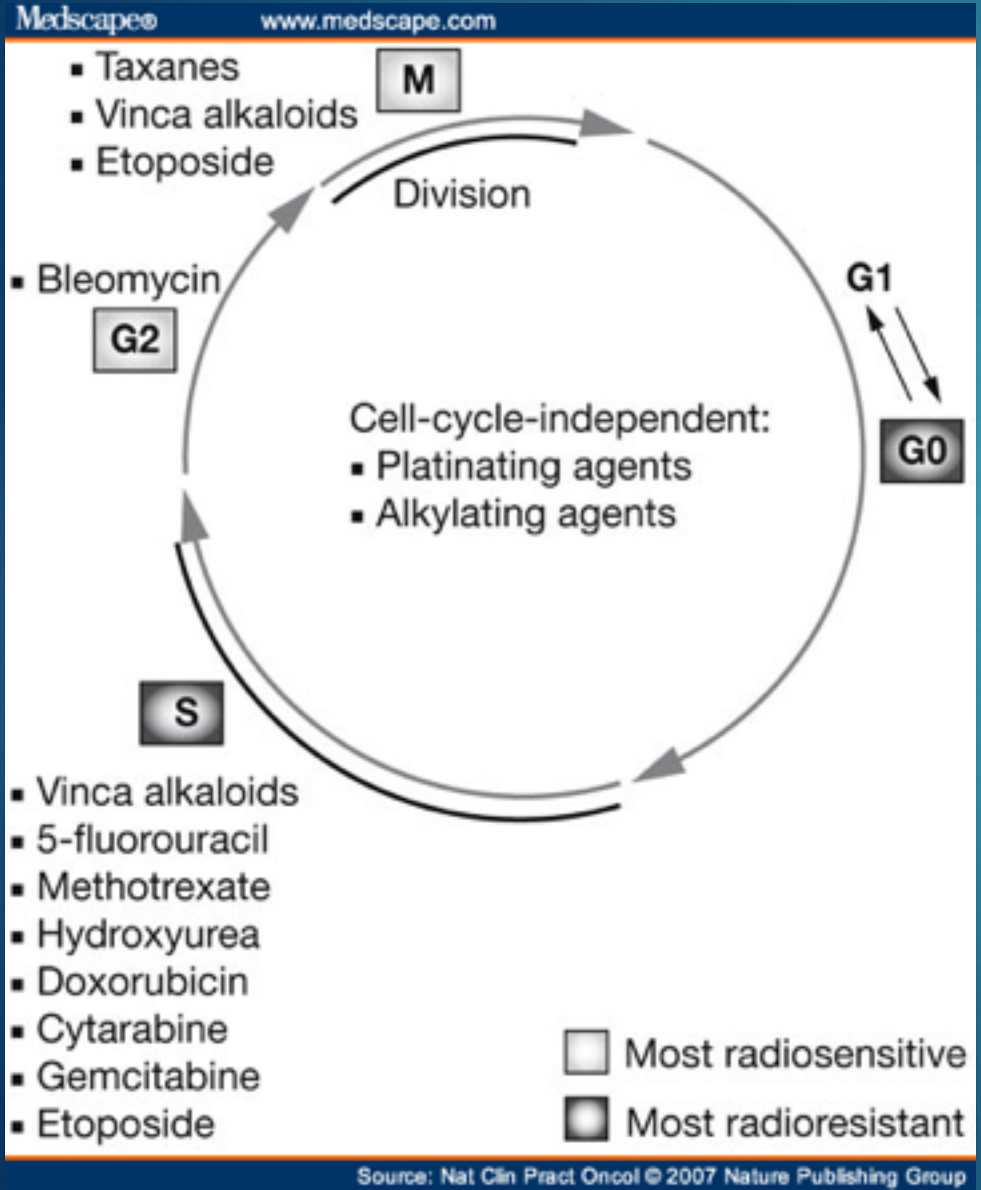
How does Chemotherapy work?

Hijacking the Process



Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition*: www.accessmedicine.com

Cell Cycle and Chemotherapy



- Few Things to note:
- Cell cycle specific drugs:
  - Drugs interfere with faster growing cells
  - S-phase (DNA synthesis) and M-phase (mitosis) are particularly important
- Cell cycle non-specific drugs:
  - Drugs that can interfere for more slow growing cells
  - Inflict damage whenever DNA is needed
    - Not just mitosis

Non-Cell Cycle Specific Chemotherapy

ALKYLATING AGENTS AND PLATINUM COMPOUNDS

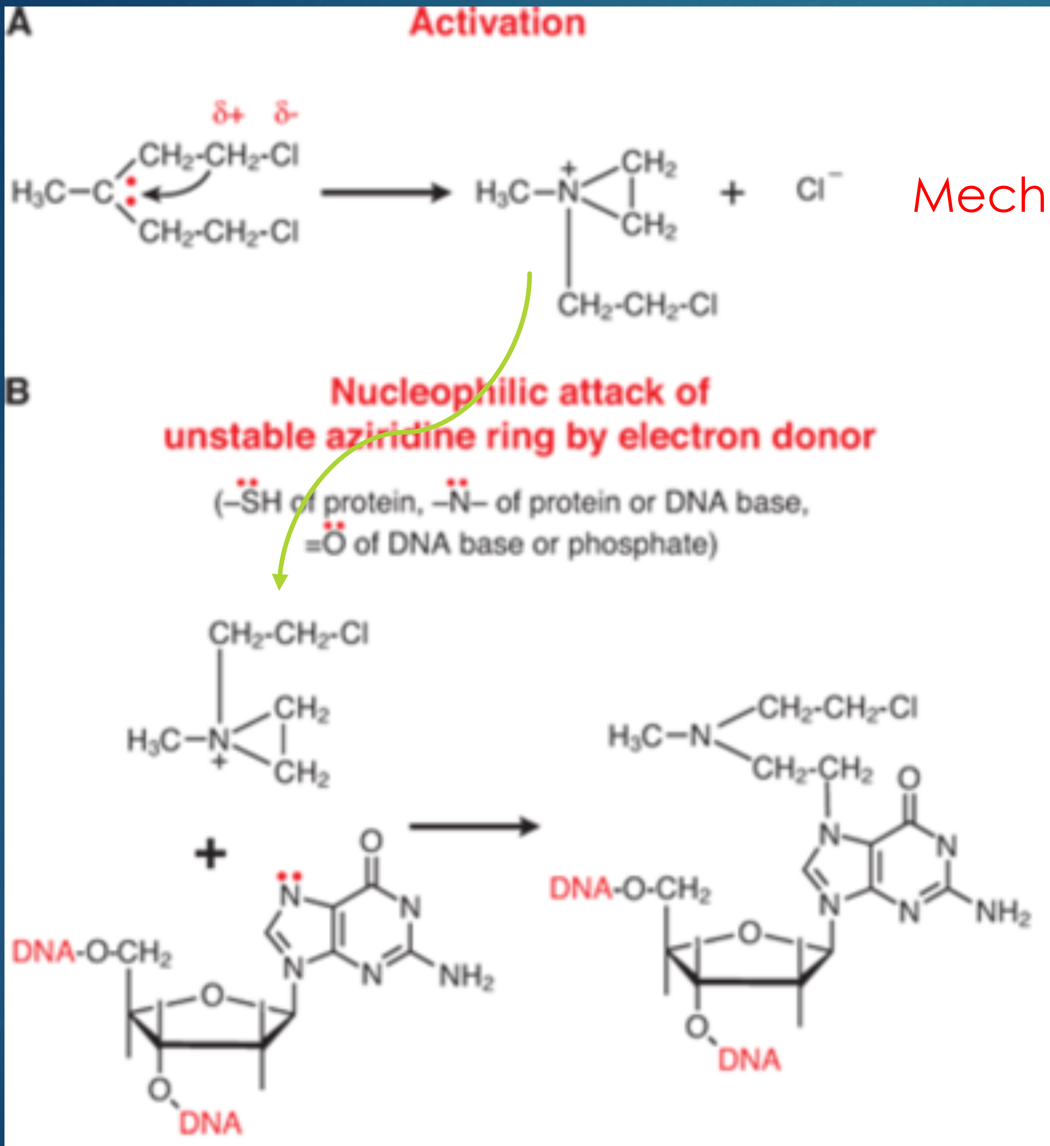
Alkylating Agents

- Heterogenous group of loosely related compounds:
  - Nitrogen mustards (Mechlorethamine, cyclophosphamide, ifosfamide)
  - Ethyleneimines (thiotepa, altretamine)
  - Alkyl sulfonates (Busulfan)
  - Nitrosureas (Carmustine)
  - Triazenes (Dacarbazine)
- MOA: Form highly reactive carbonium ion intermediates which covalently link to amines, oxygens, or phosphates of DNA
  - N7 of guanine is highly susceptible
  - Other targets include N1 and N3 of adenine, N3 of cytosine and O6 of guanine
- Cell will then either try to repair the DNA and undergo cell cycle arrest
  - In cases where this does not work it will then undergo apoptosis

Alkylating Agents

- Uses: extensive
  - Solid Tumors: Breast cancers, prostate cancers, sarcomas, etc
  - Heme malignancies: leukemias, lymphomas, myeloma
  - Non-malignant conditions: rheumatic diseases
- Commonly used with cell cycle dependent agents
- Resistance:
  - Decreased permeation of active transported drugs
  - Increased concentrations of nucleophillic substances that bind and inactivate agents
  - Increased MMR and repair mechanisms

Alkylating Agents



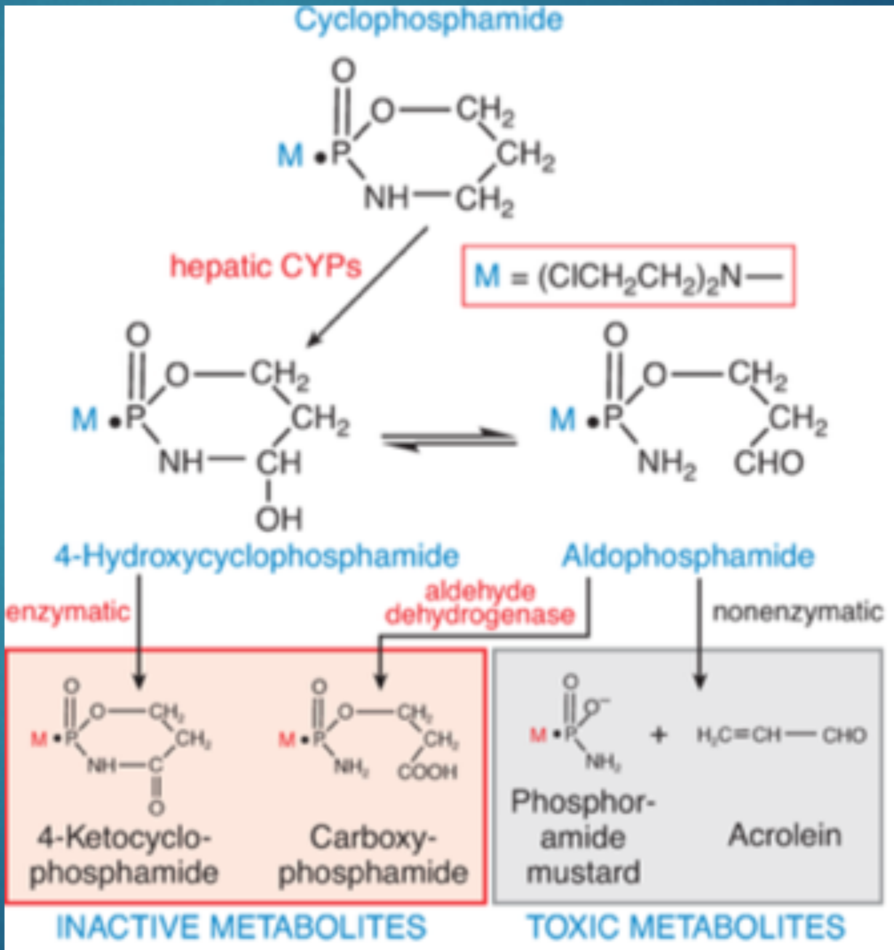
Mechlorethamine

N7 of guanine

Source: L. L. Brunton, B. A. Chabner, B. C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12ed.
www.accesspharmacy.com

Cyclophosphamide (Cytoxan)

- One of the most extensive agents used in therapy
  - Given IV and PO
- Prodrug: a drug that is converted in the body to an active metabolite
  - Phosphoramide mustard
- Acrolein is toxic and causes hemorrhagic cystitis
- Used over a variety of diseases including
  - Rheumatic disease
  - Solid tumors
  - Heme malignancies



*Similar to ifosfamide

Source: L. L. Brunton, B. A. Chabner, B. C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12ed.
www.accesspharmacy.com

Toxicities of Chemotherapy

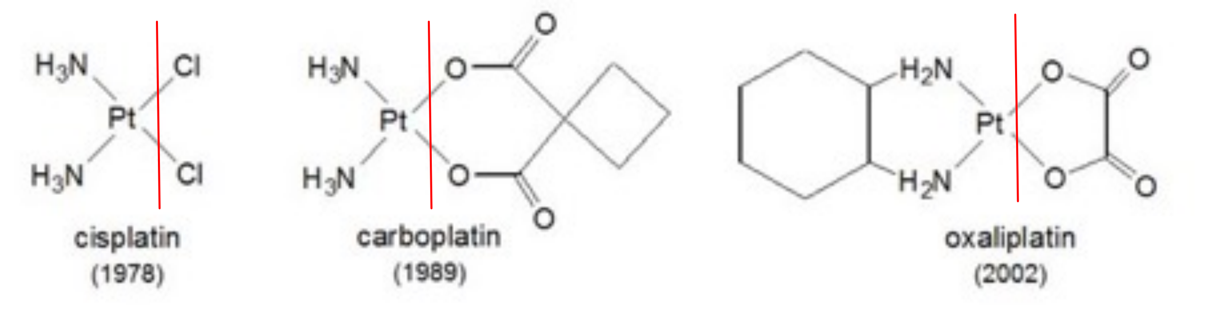
- Bone Marrow Suppression (Mostly dose-limiting): affects dose density
  - Class effect but to varying degrees
  - Can lower platelets (thrombocytopenia), white blood cells (neutropenia) and red blood cells (anemia)
    - Can be used advantageously for bone marrow transplants
  - Acute myelosuppression: nadir of 7-10 days and recovery in 14-21 days
    - Cyclophosphamide, ifosfamide
  - Delayed myelosuppression: nadir in 4 – 6 weeks with gradual recovery
    - Carmustine
  - Why the concern:
    - Thrombocytopenia: bleeding complications
    - Neutropenia: Opportunistic infections
    - Anemia: Fatigue, QOL, SOB

Toxicities of Chemotherapy

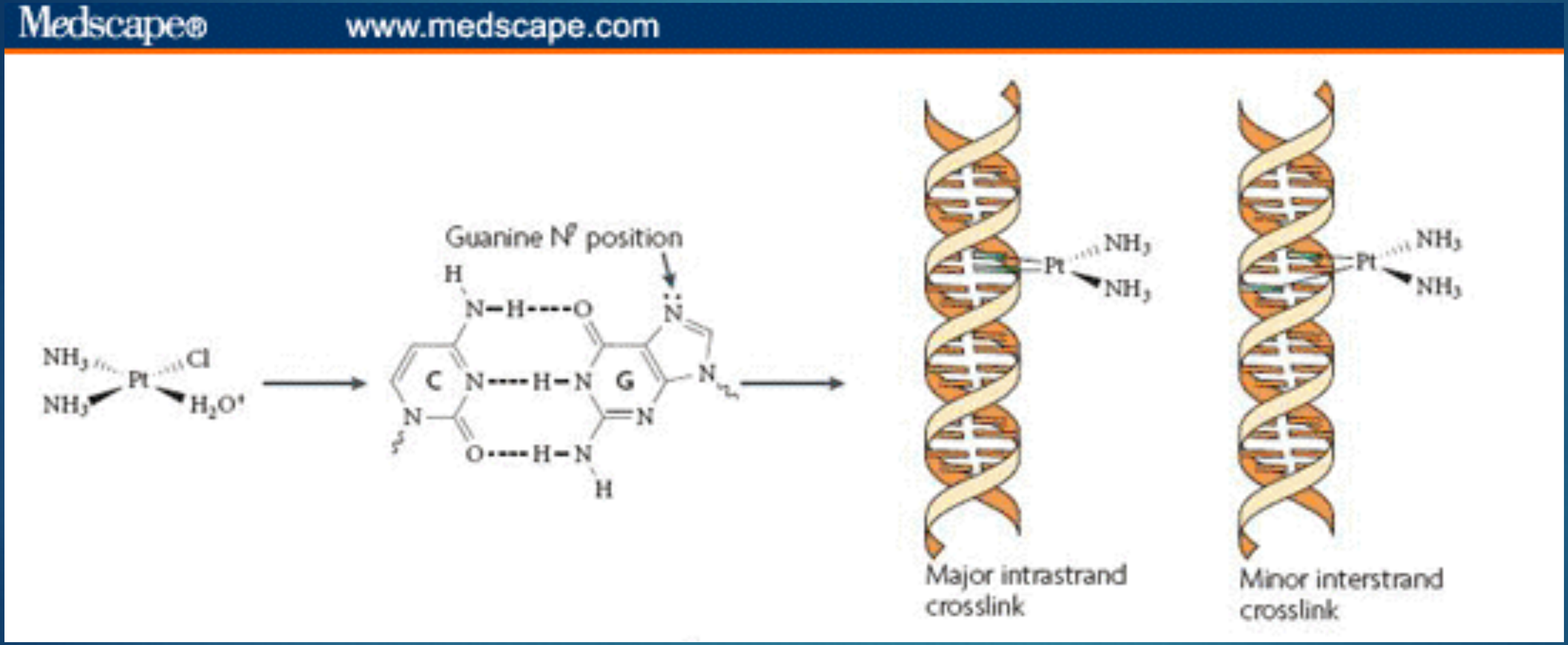
- GI Toxicity:
  - Mucosal ulceration
  - Chemotherapy Induced Nausea and Vomiting (CINV):
    - Caused by various stimuli in the body and sent via redundant pathways
    - Varies depending on agent to varying degrees
    - Divided into 4 categories: High, Moderate, Mild, Minimal
      - Treatment is based on rating
    - Can start in hours (acute) and last for days (delayed)
    - Complications: GI bleeds, dehydration/malnutrition, kidney failure, esophageal tears
  - Constipation
  - Diarrhea

Platinum Complexes

- Behave similar to alkylating agents without alkylation
- MOA: Covalently bind on nucleophillic sites of DNA
  - The chloride, cyclohexane and oxalate molecules are displaced by water leaving a highly positively charged molecule
- Cis/carboplatin share similar activity and are somewhat interchangeable
- Resistance:
  - Cis/carboplatin share cross-resistance, while oxaliplatin does not
  - Loss of function of MMR proteins which would induce protein
  - Up-regulation of DNA repair genes



Cisplatin MOA



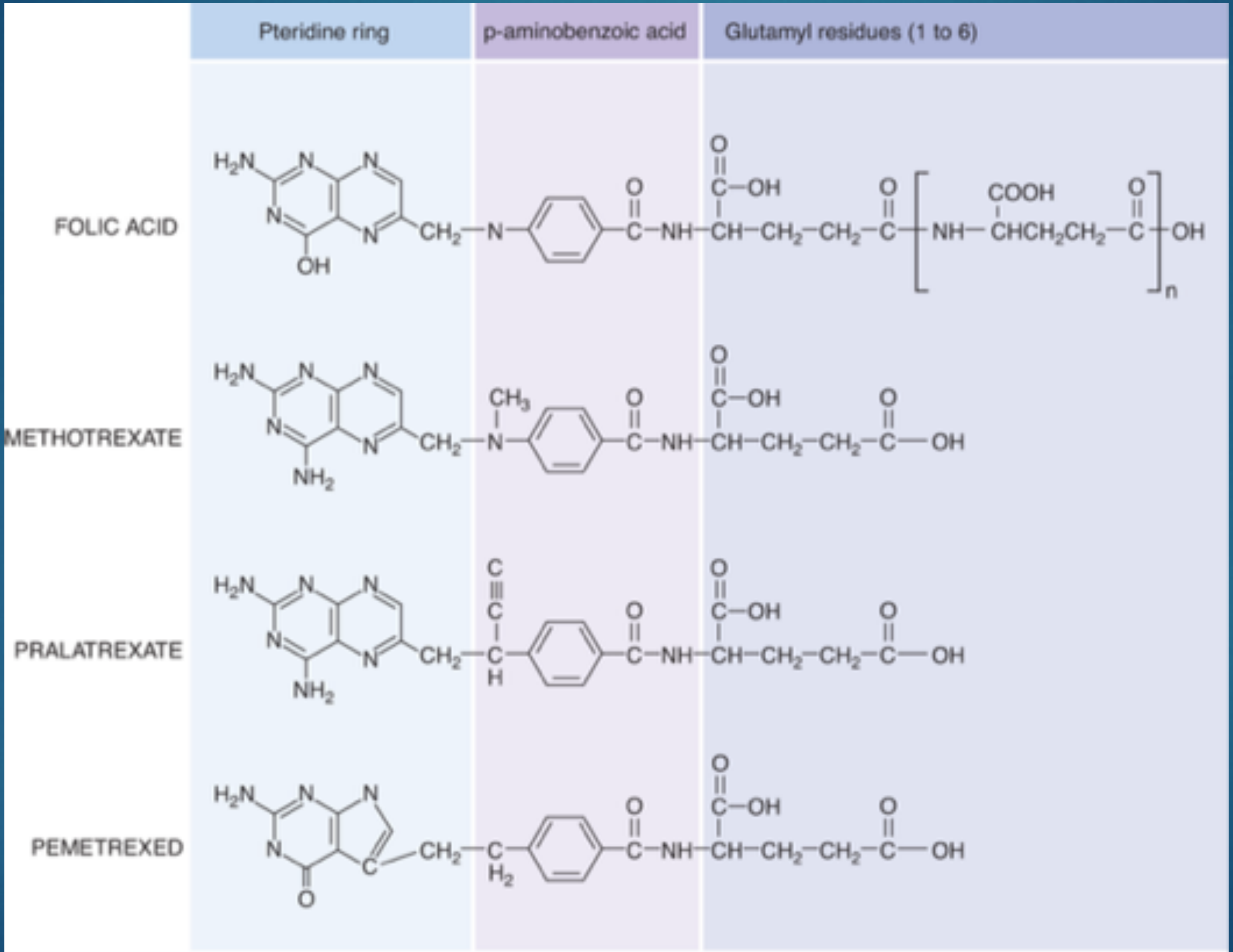
Platinum Complexes

- Spectrum of activity:
  - Cis/carboplatin: Solid tumor primarily
    - SCLC, NSCLC, Head and Neck, Bladder, Testicular
  - Oxaliplatin: GI tract cancers (Gastric, Pancreatic, CRC)
- Toxicities:
  - Cis/carboplatin:
    - N/V: Cisplatin more so
    - Renal toxicity: Cisplatin more so
    - Myelosuppression: carboplatin more so (thrombocytopenia)
  - Oxaliplatin:
    - Peripheral Neurotoxicity
    - Myelosuppression: thrombocytopenia

S-Phase: Antimetabolites

FOLIC ACID ANALOGS, PYRIMIDINE ANALOGS, PURINE ANALOGS

Antifolates

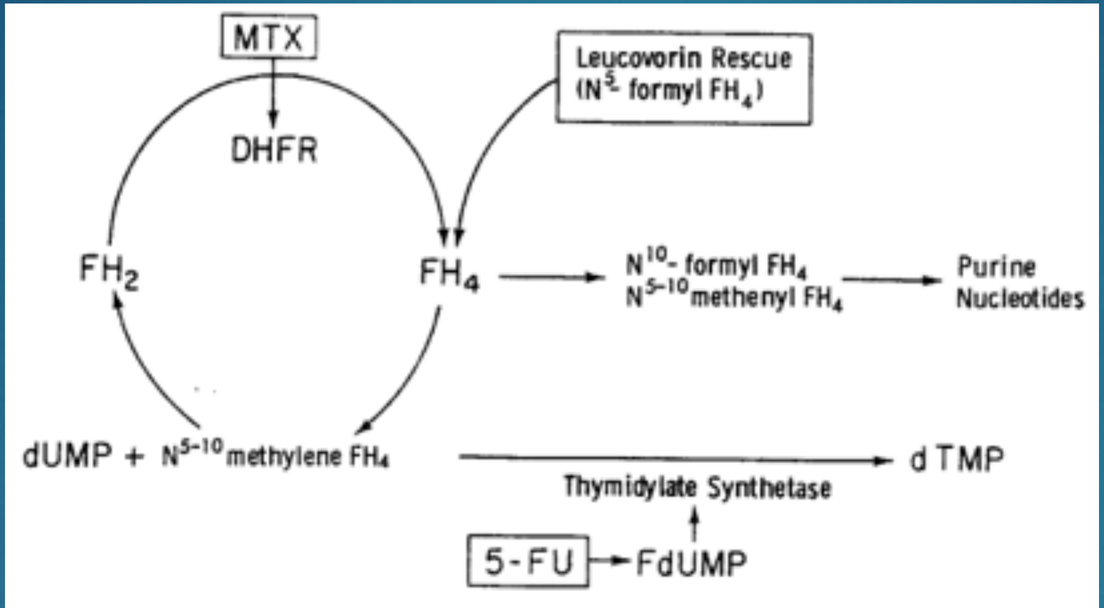


Source: L. L. Brunton, B. A. Chabner, B. C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12ed.
www.accesspharmacy.com

Antifolates (Methotrexate)

- 1948: Sidney Farber discovered aminopterin to treat childhood leukemia
- MOA: Dihydrofolate reductase (DHFR) inhibitor
  - Depletion of tetrahydrofolate, necessary for purine and thymidylate synthesis
- Resistance:
  - Decreased active transport into cell
  - Altered DHFR that impairs MTX binding or increased expression of DHFR
  - Increased efflux and active transport out of cells
- Side Effects:
  - Myelosuppression
  - Mucositis and intestinal inflammation
  - Nephrotoxicity
  - Neurotoxicity

Methotrexate MOA



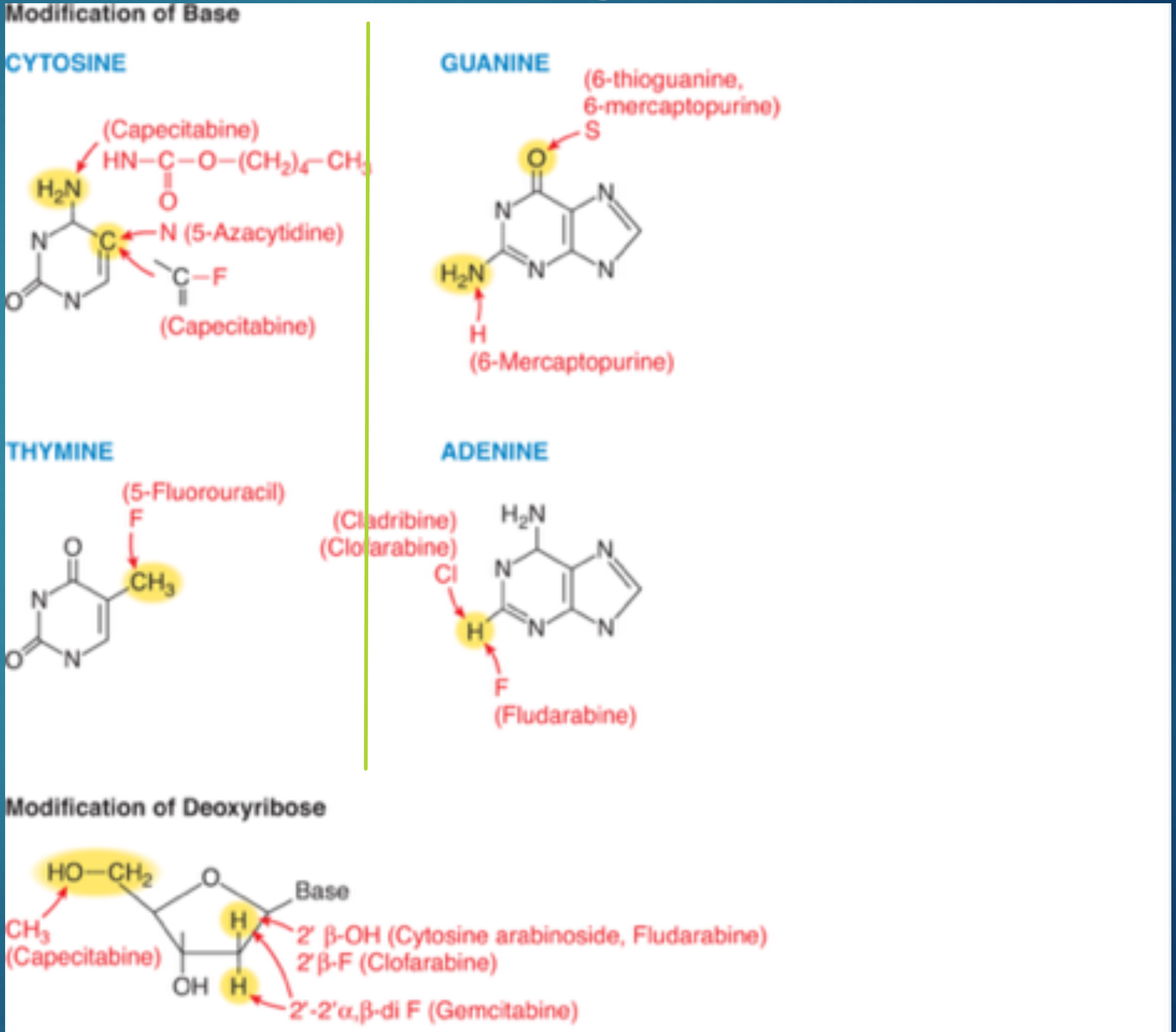
- FH_2 is reduced by DHFR to FH_4 (needed for purine synthesis)
- MTX blocks DHFR which increases FH_2 polyglutamate (cytotoxic)
- Deoxyuridine monophosphate (dUMP) is converted to thymidine monophosphate(dTMP) (component of DNA)
- Leucovorin, an antidote can replete FH_4 stores and continue cycle
  - Used in poisonings and to high-dose MTX rescue

Methotrexate Uses

- Used in all types of cancers and include autoimmune conditions as well
  - Control graft-versus-host disease
- Doses can be given orally, intravenously or intrathecally
- High-Dose Methotrexate (> 1 g/m^2/dose)
  - Requires therapeutic blood monitoring
  - Use of leucovorin "rescue"
  - Requires urine alkylinization
  - Penetrates CNS
    - Think large molecule, and blood-brain barrier

Pyrimidine & Purine Analogs

- Right is the pyrimidines
- Left is purines
- In theory:
  - Looks close enough to each that it can be substituted
  - They can be combined together and with antifolates in therapy
    - ALL regimens use various combinations
    - Considerable toxicities



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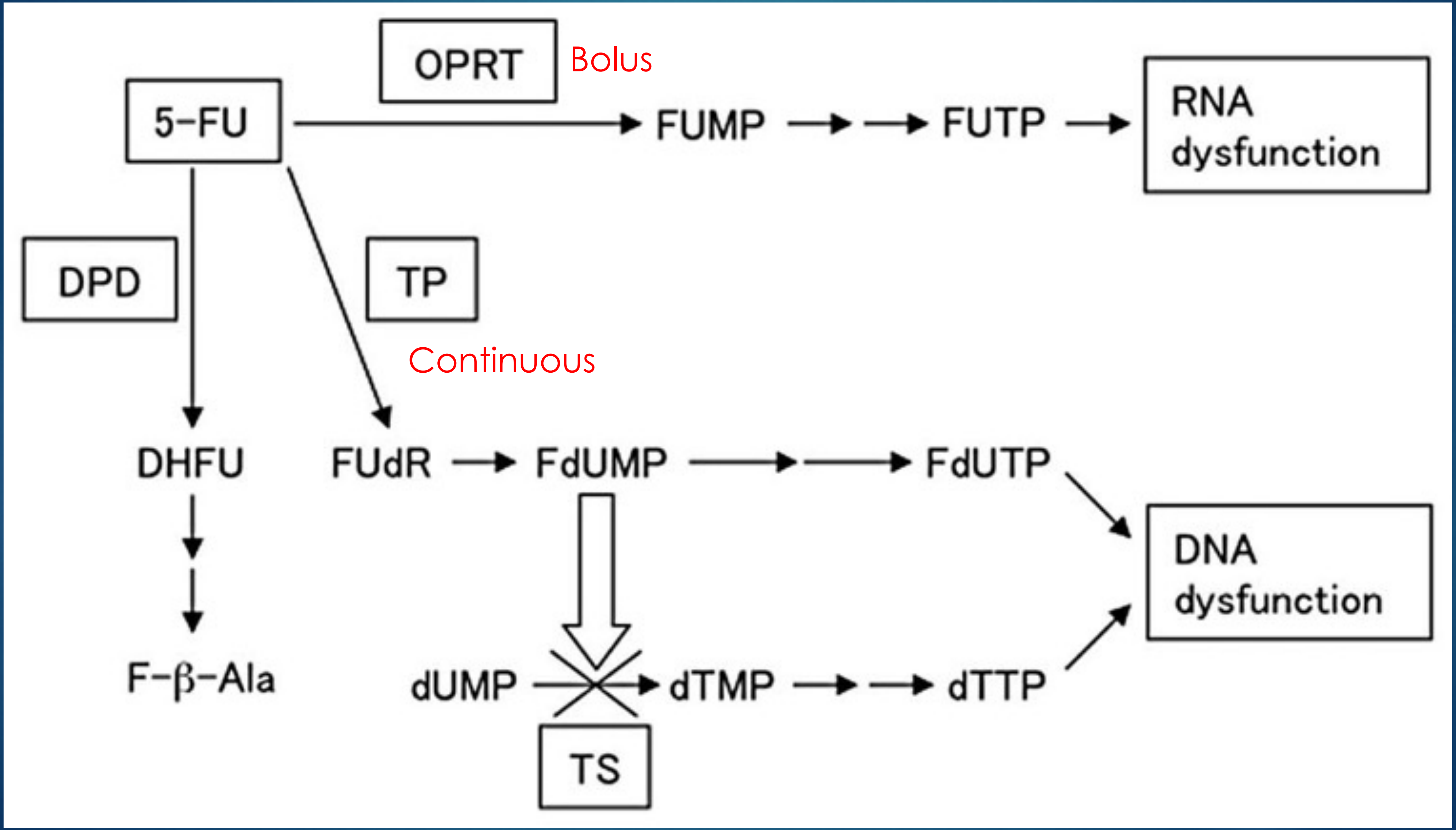
5-Fluorouracil: Pyrimidine Analog

- MOA: Prodrug, is somewhat rate dependent (depends how it is administered)
  - Continuous infusion: inhibition of thymidylate synthase leading to thymidine deficiency
    - Leucovorin is administered prior to starting to stabilize 5FU-TS complex
  - Bolus: False base integration into RNA and DNA
- Pharmacogenomics: Clearance is mediated through dihydyropyrimidine dehydrogenase (DPD)
  - Polymorphic
- Resistance:
  - Reduced conversion to active metabolite
  - Amplification of TS or alteration of TS binding site
  - Amplificiation of degrative enzymes

5-Fluorouracil MOA



5-Fluorouracil in Practice

- Colon cancer: FOLFOX regimen (developed at RPCI):
  - Oxaliplatin 85 mg/m^2 IV on day 1
  - Leucovorin 400 mg/m^2 IV given with oxaliplatin on day 1, followed by
  - 5-FU 400 mg/m^2 IV Bolus, then
  - 5-FU 2.4 g/m^2 IV given continuously over 46 hours
- Side effects:
  - Bolus: myelosuppression, angina
  - Continous: N/V, diarrhea, mucositis, hand-foot syndrome
- Antidote: uridine triacetate

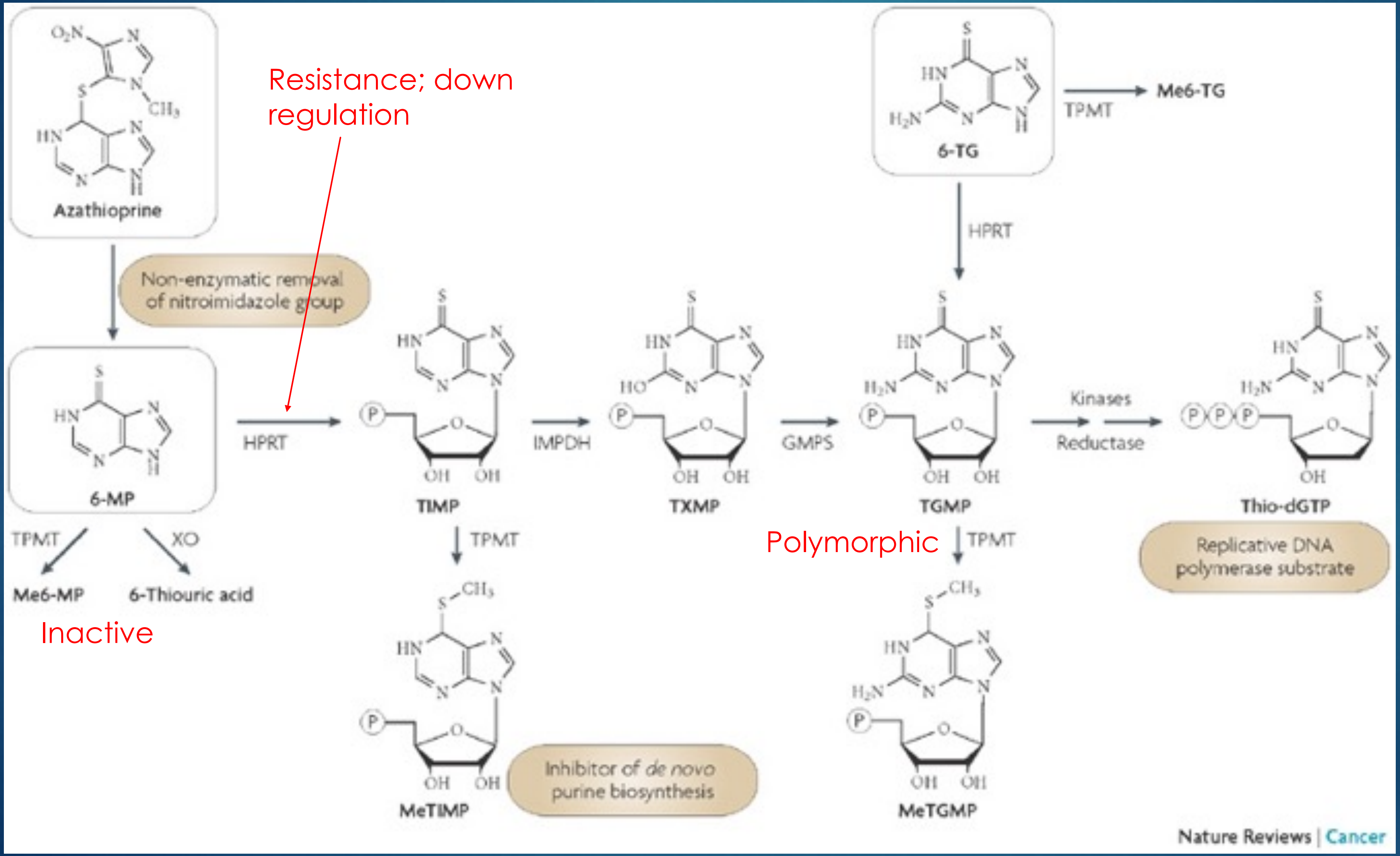
Cytarabine: Pyrimidine Analog

- Cytosine arabinoside (ara-C)
- MOA: Prodrug converted to ara-C-TP, false base integration into DNA leading to polymerase inhibition
- Side Effects: Dose dependent
  - Myelosuppression and rash
  - High dose (> 1 g/m^2 per dose)
    - Cerebellar syndrome
    - Conjunctivitis

6-Mercaptopurine: Purine Analog

- Developed in 1953 and used by Sidney Farber to treat pediatric ALL
  - Still used today
- MOA: inhibits purine synthesis and false integration into DNA or RNA
- Side Effects:
  - Hepatotoxicity
  - Myelosuppression

6-MP MOA


Azathioprine
Non-enzymatic removal of nitroimidazole group
6-MP
HPRT
TIMP
IMPDH
TXMP
GMPS
TGMP
Kinases
Reductase
Thio-dGTP
Replicative DNA polymerase substrate
6-TG
TPMT
Me6-TG
HPRT
TPMT
XO
Me6-MP
6-Thiouric acid
TPMT
MeTIMP
Inhibitor of de novo purine biosynthesis
TPMT
MeTGMP
Nature Reviews | Cancer
Resistance; down regulation
Polymorphic
Inactive

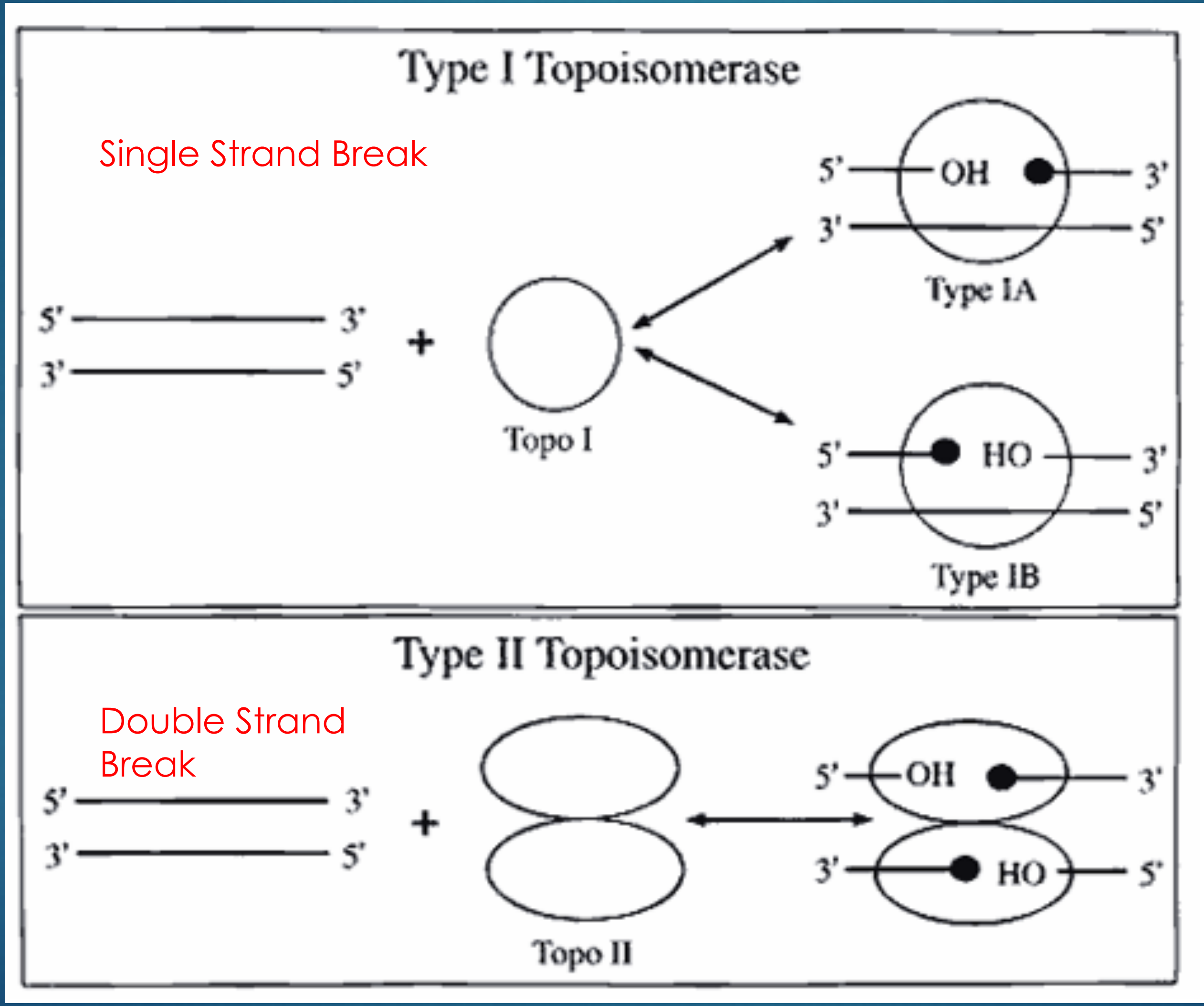
TPMT & Genomics

- 11% of caucasians have decreased TPMT activity
  - TPMT*1: WT allele (fully active)
  - TPMT*2, 3A, 3C: reduced function alleles
- Loss of function alleles increase overall response but significantly increases myelosuppression
- Testing is therefore warranted when sever myelosuppression with standard 6-MP doses

Natural Products

EPIPODOPHYLLOTOXINS, TAXANES, VINCA ALKALOIDS, CAMPTOTHECANS

Topoisomerase



Anthracycline: Doxorubicin

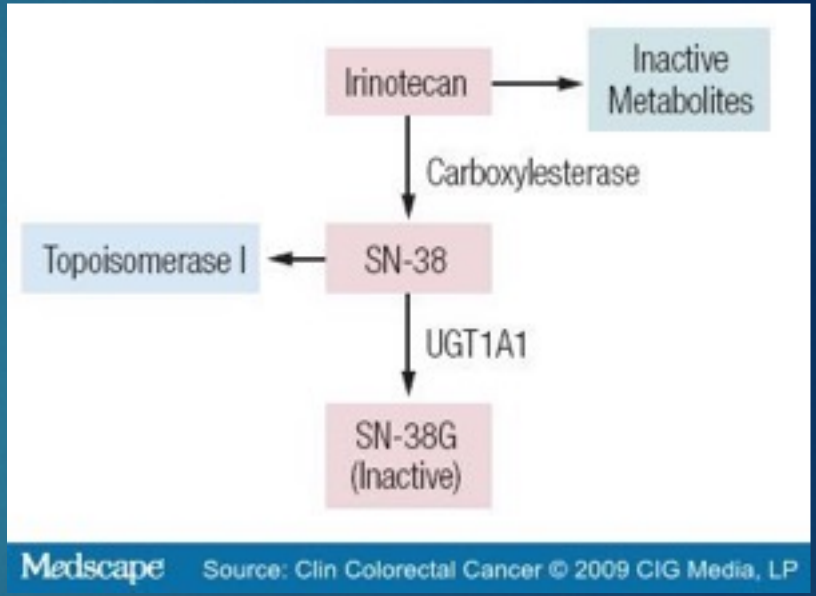
- Antracyclines: anti-tumor antibiotics, isolated from *S. peucetius*
  - Class includes: daunorubicin, epirubicin, idarubicin
- MOA: Multiple. Prodrug (doxorubicinol)
  - Major: Topoisomerase II inhibition- prevents re-ligation of DNA
  - Minor: DNA intercalation, and prevention of free radical formation
- Resistance: Upregulation of P-gp (MDR1) that effluxes doxorubicin out
- Side Effects:
  - Cardiotoxicity (additive effects with concurrent cyclophosphamide)
    - Lifetime dosing limits
  - Myelosuppression
  - Alopecia
  - Mucositis/ N/V
  - Vesicant
  - Red discoloration of: urine, tears, CNS fluid

Etoposide

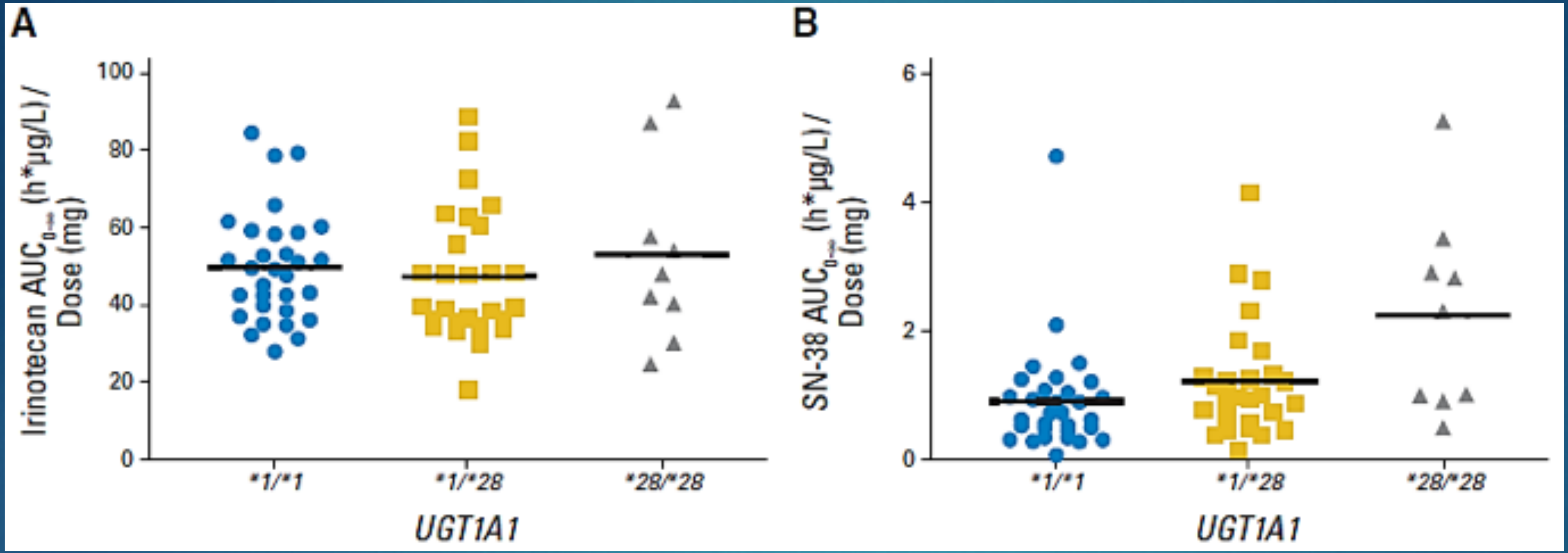
- Extract from roots of *Podophyllum peltatum* (mandrake plant)
- MOA: Topoisomerase II inhibitor via stabilization of TOP2 complex
  - Accumulation of cells in S phase (G_2 Phase as well)
  - Leads to apoptosis
- Side Effects:
  - Myelosuppression
  - Alopecia
- Resistance:
  - P-gp up-regulation
  - Repair of DNA breaks
  - Alterations to Topoisomerase II

Irinotecan

- Isolated from a Chinese tree *Camptotheca acuminata*
- MOA: Prodrug, Topoisomerase I inhibition
  - Active metabolite is SN-38
  - SN-38 is inactivated via UGT1A1
- Side effects:
  - DIARRHEA
  - Alopecia
  - Myelosuppression
- Resistance:
  - P-gp upregulation



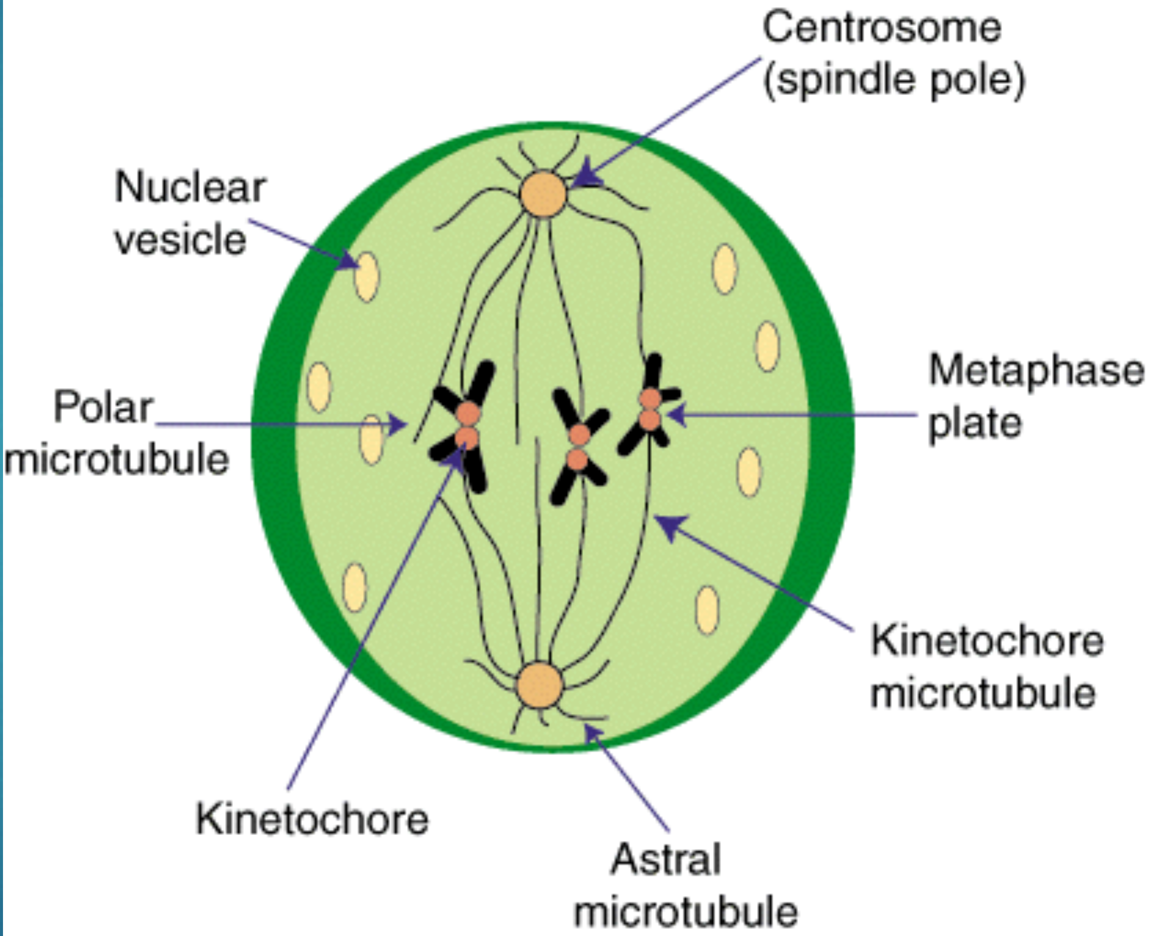
Irinotecan and UGT1A1



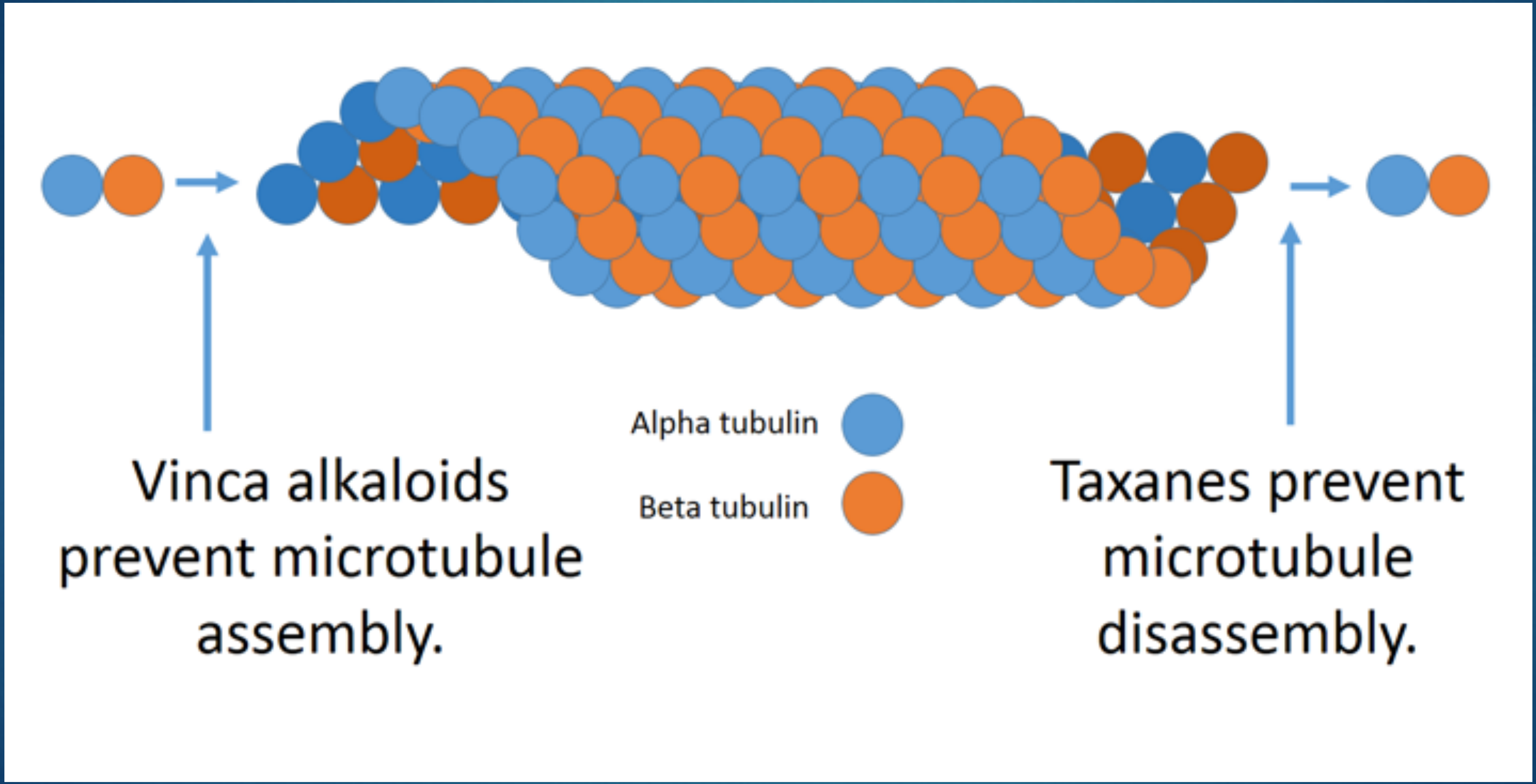
- UGT1A1 is polymorphic, 10% of patients are homozygous for *28
- *28 is loss of function allele, increased severity of diarrhea
  - Can last for days
- Heterozygous patients also have more profound diarrhea

Antimitotic Agents

- Building blocks of microtubules consist of two subunits, an [illegible] and a β
- Microtubules grow from the spinal pole towards the metaphase plate
  - Repetitive assembly of both subunits
- Microtubules bind to kinetochore and then disassemble back to the spindle pole
- Drugs that target mitosis target microtubules
  - Assembly
  - Disassembly



Taxanes vs Vincas



Taxanes: Polymerizing agents

- Discovered from *Taxus brevifolia* (Pacific Yew Tree)
- MOA: Inhibit depolarization by binding to β-tubulin, causing mitotic arrest
  - Paclitaxel, docetaxel, cabazitaxel, ixabepilone, nab-paclitaxel
- Drugs are extremely hydrophobic, use castor oil for dissolution
  - Caster Oil causes anaphylactic reactions
- Side Effects:
  - Myelosuppression
  - Alopecia: full body
  - Neuropathy
  - Myalgias
  - Edema
- Resistance:
  - P-gp up-regulation (substrate)
  - Alteration of tubulin structure

Vinca Alkaloids: Depolymerization

- Isolates from *Catharanthus roseus* (Madagascar periwinkle)
- MOA: Inhibition of polymerization by binding to β – tubulin and stabilizing it
  - Vincristine, vinblastine, vinorelbine
- Fatal if given intrathecally (No vines in the spine!)
- Side Effects:
  - Vesicant
  - Neurotoxicity: Vincristine
    - Peripheral neuropathy
    - GI: constipation
  - Myelosuppression: Others
- Resistance:
  - P-gp upregulation

Activities…

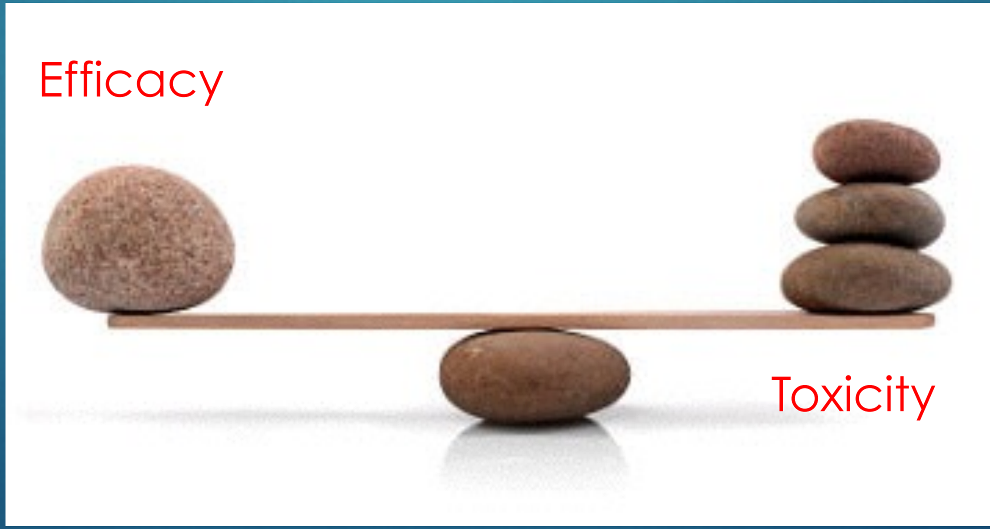
- Heme Malignancies:
  - Leukemia: Anthracyclines (doxorubicin), cytarabine, fludarabine, vincristine, etoposide, cyclophosphamide
  - Lymphoma: Ifosfamide, cyclophosphamide, methotrexate, cisplatin, vincristine, doxorubicin
- Solid Tumors:
  - GI: 5-Fluorouracil, oxaliplatin, irinotecan
  - Breast: cyclophosphamide, methotrexate, doxorubicin, taxanes, platinum
  - Lung: Cisplatin, etoposide, taxanes, pemetrexed, gemcitabine
  - Prostate: taxanes

Synopsis

- These are "traditional" chemotherapeutic agents
- Agents can be used in a variety of cancers
- Members of the same drug class can have a different side effect profile
- Regimens are combinations of multiple mechanisms of action
  - Also balancing of side effects
- Drugs administered in different ways can alter their effects in the body
- Drugs respond differently in different patients
  - Change in toxicity profiles
- Side effects can be dose dependent

Chemotherapy Regimens

- Agents *obviously* need to be active against a given tumor
- Select agents with different:
  - MOA
  - Resistance
  - Dose-limiting toxicity
- Combinations needed to maximize kill and limit resistance
  - Remember principles



Putting it all together… A regimen

- Regimen known as CHOP is a cure for lymphomas even in stage IV
- C: Cyclophosphamide: alkylation of DNA (non-specific)
  - Myelosuppression, NV, Renal dysfunction, alopecia
- H: Doxorubicin: Topoisomerase II inhibitor (S-phase)
  - Cardiotoxicity, NV, myelosuppression, mucositis
- O: Vincristine: Antimitotic agent (M-Phase)
  - Neuropathy
- P: Prednisone: Not covered but immunosuppression
  - Increased appetite, hyperglycemia, hypertension
- Note the mechanisms of actions of the agents
  - Note the toxicities as well

As time goes by…

- Traditional agents = indiscriminate killer of cells
  - How do we know good cells from bad cells?
  - Assumes that ALL rapidly dividing cells are bad
  - Assumes that ALL slow dividing cells are good
- Drug development has had some serendipitous discoveries:
  - 1980s: All-transretinoic acid (ATRA) in APL
    - Targets immature leukemic cells and causes differentiation to force differentiation
  - 1980s: Tamoxifen in hormone positive breast cancer
    - Targets cells that over-express ER/PR
- Therapy is moving towards more targeted approaches
  - Moving from carpet-bombing to tactical bombing

Targeted Therapy

- More appropriately termed, molecularly targeted therapies
  - Target specific genes, proteins or tissue environments
- Specific to subtypes of cancer
  - Requires an understanding of cancer pathophysiology
  - Requires genotyping and effecting signal pathways
- What makes a good target?
  - Targets only present on/in cancer cells
  - Targets more commonly found on/in cancer cells
  - Or target both cancer and normal, but normal cells that regenerate

Small Molecule Inhibition

- AKA Tyrosine kinase inhibitors (TKI)
  - Intracellular monoclonal antibodies
- Tyrosine kinase: phosphorylate from ATP tyrosine, serine and threonine, signaling pathway for survival and proliferation
  - Deregulation by various means is one way cancer cells survive
- Class of drugs mainly acts through competitive inhibitors of the ATP-binding domain
- May also target other downstream enzymes active in signal transduction
  - RAS
  - RAF

4 Key Issues

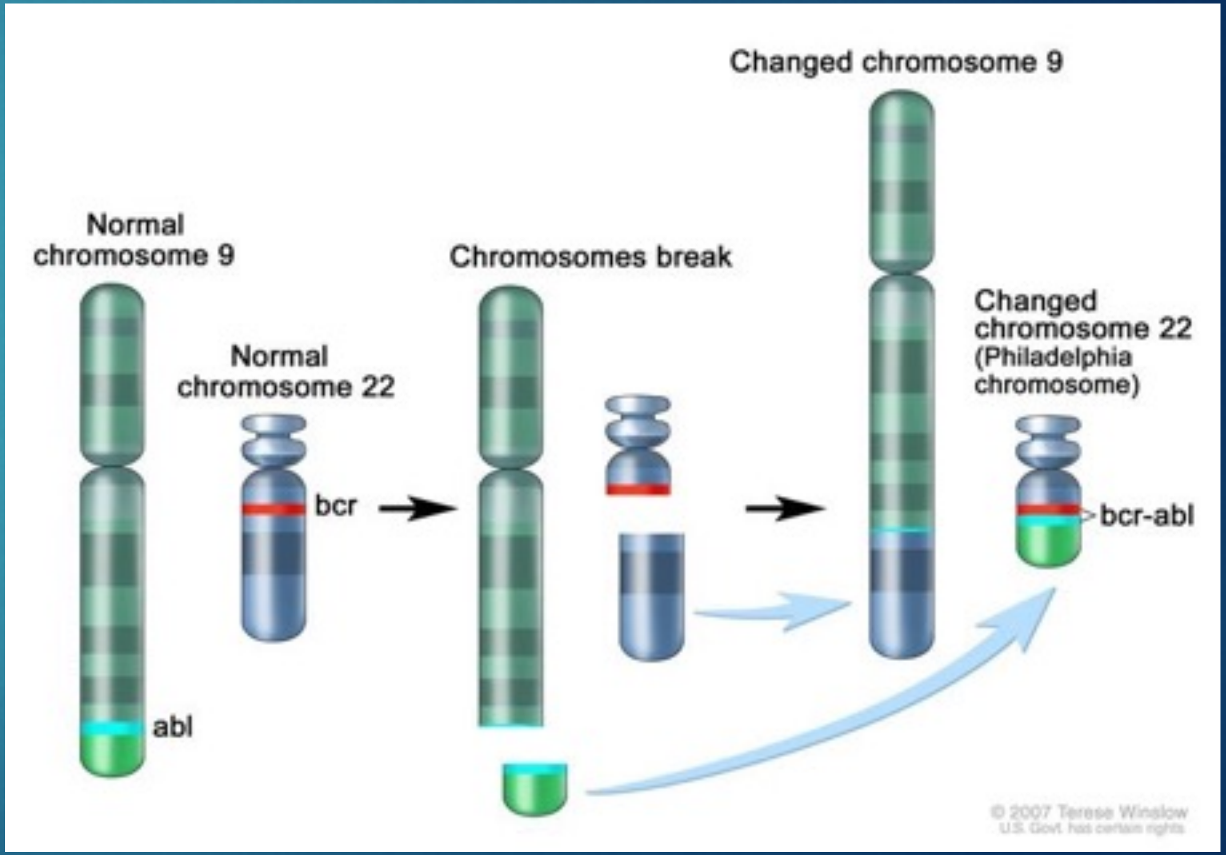
- 4 issues with these drugs to consider:
  - Interactions with CYP 3A4: Drug interactions
    - Interaction with P-gp (MDR1)
  - Administration with or without food
    - Food interactions can cause either an increase or decrease in exposure
  - Acidity of the stomach
    - Drugs that effect acidity (PPIs and H2 Blockers)
  - Compliance
    - Patients need to take their medication

Chronic Myelogenous Leukemia

DEATH SENTENCE TO SUCCESS STORY

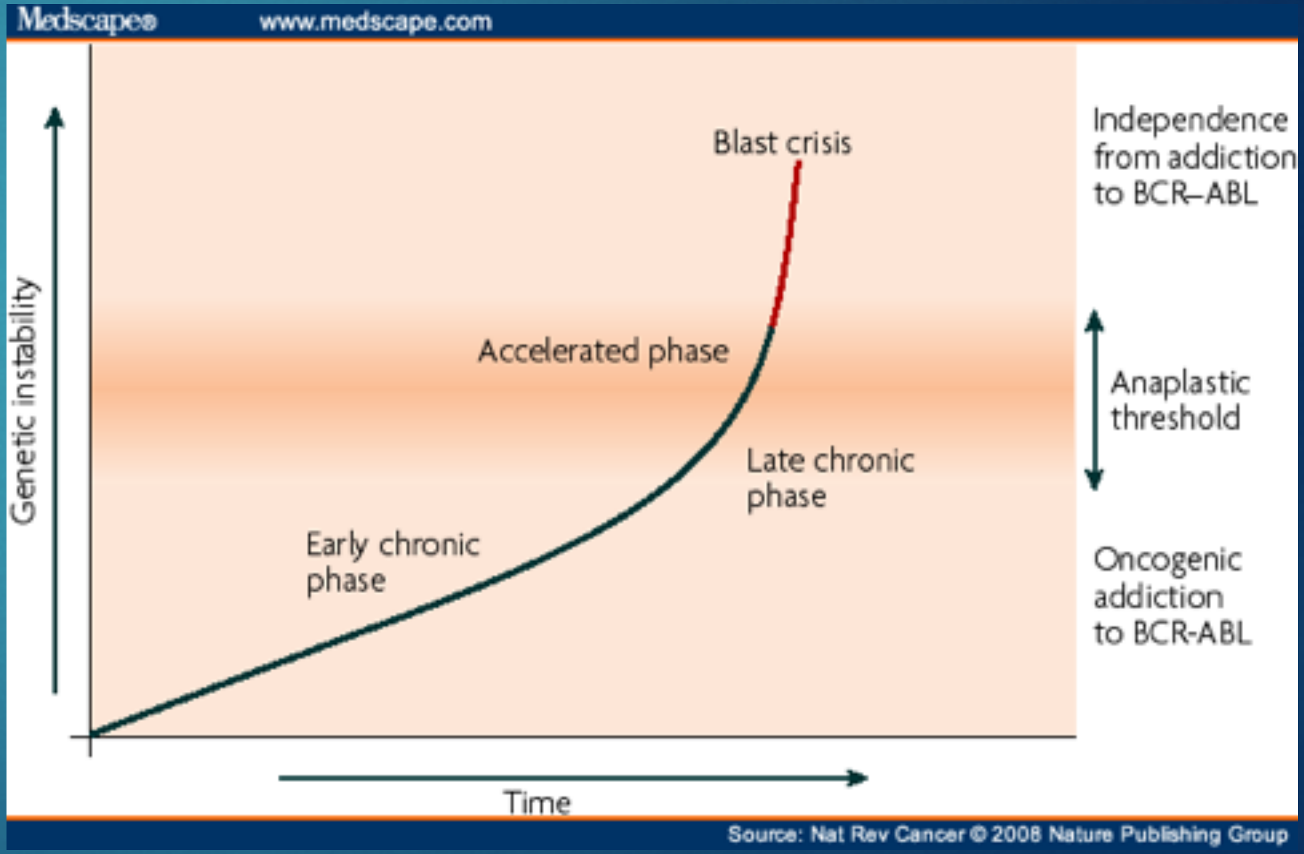
Philadelphia chromosome t(9:22)

- Translocation of the long arms of chromosomes 9 & 22 called Philadelphia Chromosome (Ph+)
  - Abelson murine leukemia gene (ABL)
  - Breakpoint cluster region (BCR)
- Forms fusion oncogene BCR-ABL
- ABL contains TK p210 that regulates proliferation
- BCR-ABL is a TK that is cytokine independent on-signal
- This is there 95% of time



CML Phases

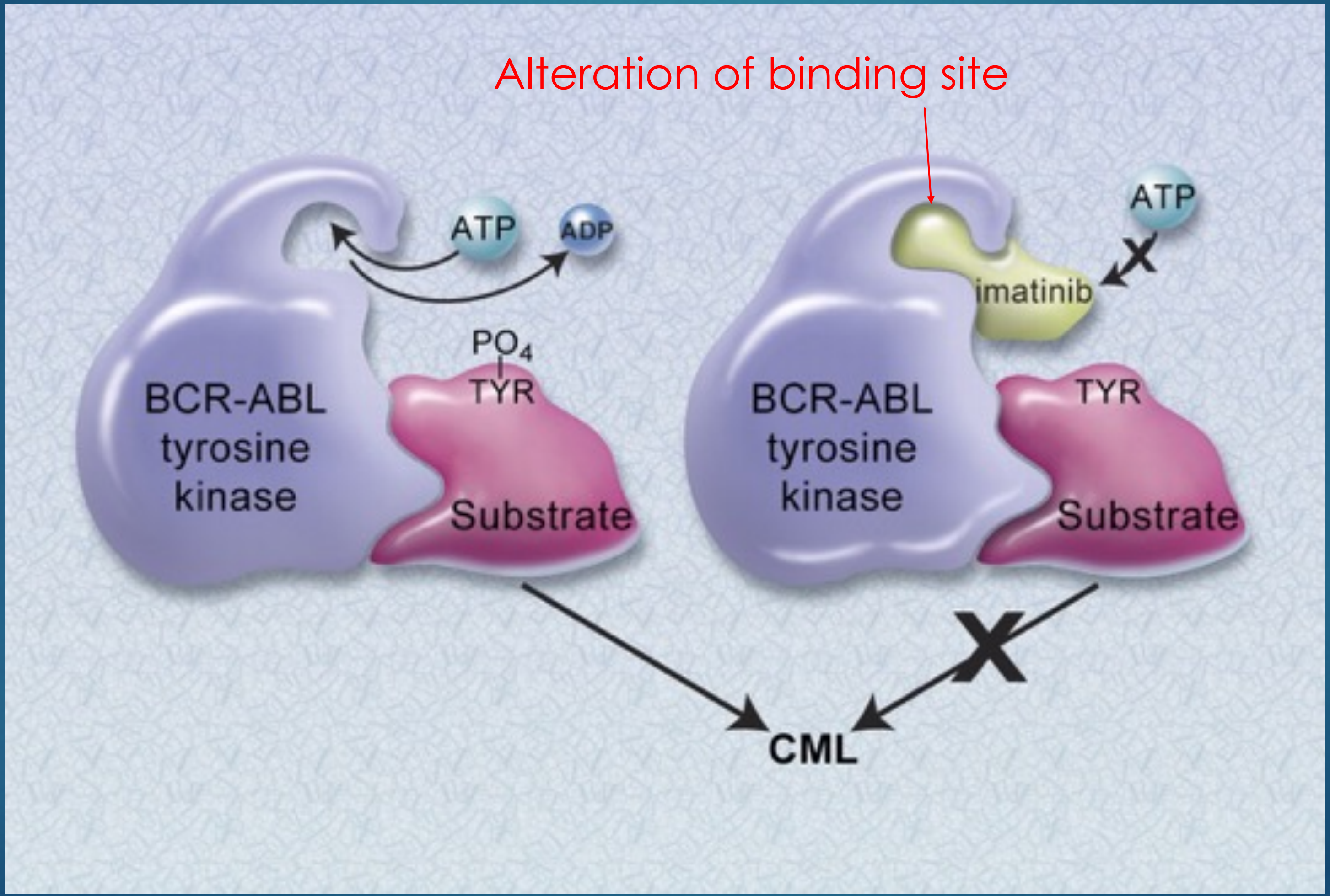
- Chronic Phase (3-5 years)
  - Asymptomatic
- Accelerated Phase (months)
  - Blasts 10 – 19 %
  - Platelets < 100,000 or > 1,000.000
  - Clonal evolution: extra abnormalities accumulate
  - Non-specific symptoms: fatigue, night sweats, fever
- Blast Crisis (~ 1 year)
  - Blasts > 20% (ALL or AML type leukemia)
  - Extramedullary blast proliferation



Imatinib (Gleevec)

- 1st agent in class, revolutionized CML treatment
- MOA: Inhibition of BCR-ABL tyrosine kinase active conformation (Philadelphia Chromosome + CML)
  - Also targets: SRC, c-KIT kinases, PDGFR (Multikinase)
- Side effects:
  - Edema, rash, nausea, myalgias
  - Myelosuppression, hepatotoxicity
- Resistance:
  - BCR-ABL kinase binding domain mutations
  - Overamplification

Imatinib


Alteration of binding site
ATP
ADP
BCR-ABL tyrosine kinase
PO4
TYR
Substrate
ATP
imatinib
BCR-ABL tyrosine kinase
TYR
Substrate
CML

TKI Class side effects

Table 9. Suggestions for management of unique TKI toxicities.[3, 43, 69-73]

Toxicity	Management Strategy
Neutropenia	Hold until recovery, potential dose reduction Myeloid growth factors may be considered
Anemia	ESAs not supported in patients with myeloid malignancies.
Thrombocytopenia	Hold until recovery, potential dose reduction
Rash	Topical or systemic steroids Dose reduction, interruption or discontinuation

Dasatinib (Sprycel)

- 2nd generation BCR-ABL inhibitor; 325 times more potent then imatinib
- MOA: Bind to active and inactive conformations of ABL kinase domain
  - Active in nearly all BCR-ABL mutations resistant to imatinib (except T315I)
- Dose: Chronic Phase: 100 mg po daily
- Pearls:
  - Can be used first line or after progression
  - Cannot use proton pump inhibitors or H2 blockers (gastric reflux agents)
- Toxicities unique to dasatinib:
  - Pulmonary arterial hypertension: D/C therapy
  - Edema (pleural effusion, pericardial, ascites)

Nilotinib (Tasigna)

- 2ND Generation BCR-ABL TKI, 30 times more potent inhibitor than imatinib
- MOA: Binds to closed conformation and exhibits a higher affinity and better fit than imatinib
  - Also inhibits c-KIT and PDGFR
- Dose: Chronic 300 mg PO **twice daily**
- Pearls:
  - Can be used first line or after progression
  - Monitor EKG with QTc, monitor electrolytes
- Toxicities unique to nilotinib:
  - QTc prolongation (cardiac arrhythmias)
  - Elevation of serum lipase
  - Hepatic toxicity
  - Peripheral arterial occlusive disease

Initial selection of TKI therapy

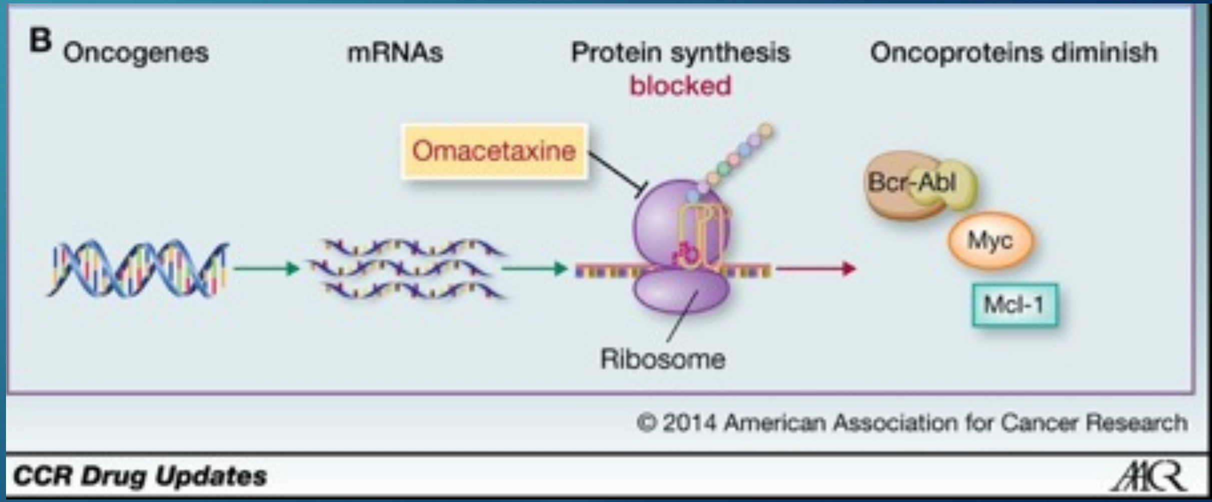
- Potency differences do not change overall survival
- Choose ONE: imatinib, dasatinib, nilotinib, considering:
  - Toxicities
  - Age or ability to tolerate therapy
  - Comorbid conditions
  - Risks
- 2nd generation have faster time to response but long-term survival is not established yet
- Progression or lack of effect, move to one of the other agents (except imatinib) or:
  - Bosutinib

bosutinib

- 2nd Generation TKI, 200 times more potent than imatinib and has activity in imatinib, dasatinib and nilotinib resistance
- MOA: Inhibition of BCR-ABL and SRC, Lyn and Hck kinases
- Dose: 500 mg PO daily
- Pearls:
  - Failed to beat imatinib in head to head first line, therefore reserved for treatment failure
  - PPI decrease concentrations
- Toxicities unique to bosutinib:
  - Hepatic toxicity
  - Diarrhea

Third line therapy and beyond

- A second or third TKI may be considered
  - Again, if imatinib is not used first line, it can't be used after failure of other agents
- Allogeneic stem cell transplant
- Omacetaxine (Synribo): indicated in failure or intolerance of TWO or MORE TKIs:
  - *Cephalotaxus harringotonia* alkaloid that binds to reversible ribosomal proteins
  - Does not bind to BCR-ABL
  - Give twice daily Sub-Q, limits compliance:
    - 1.25 mg/m2 SQ twice daily x 14 days/ 28 days



T315I CML

- Clinical Trial?
- Omacetaxine can be used (MMR 19% patients, clone reduced to LLQ 61%)
- Ponatinib (Iclusig): Indicated ONLY in T315I mutations or in those where no other TKI is indicated
  - Black Box Warning: Increased frequency of life-threatening clots and narrowing of blood vessels
  - Only available through ARIAD PASS special access program for vascular occlusion, CHF and hepatotoxicity
- MOA: Inhibits BCR-ABL as well as VEGFR, FGRF, PDGRF, EPH, SRC, KIT, RET, TIE2, FLT3
  - Explains side effects
- Dose: 45 mg PO daily
  - Avoid PPIs with these

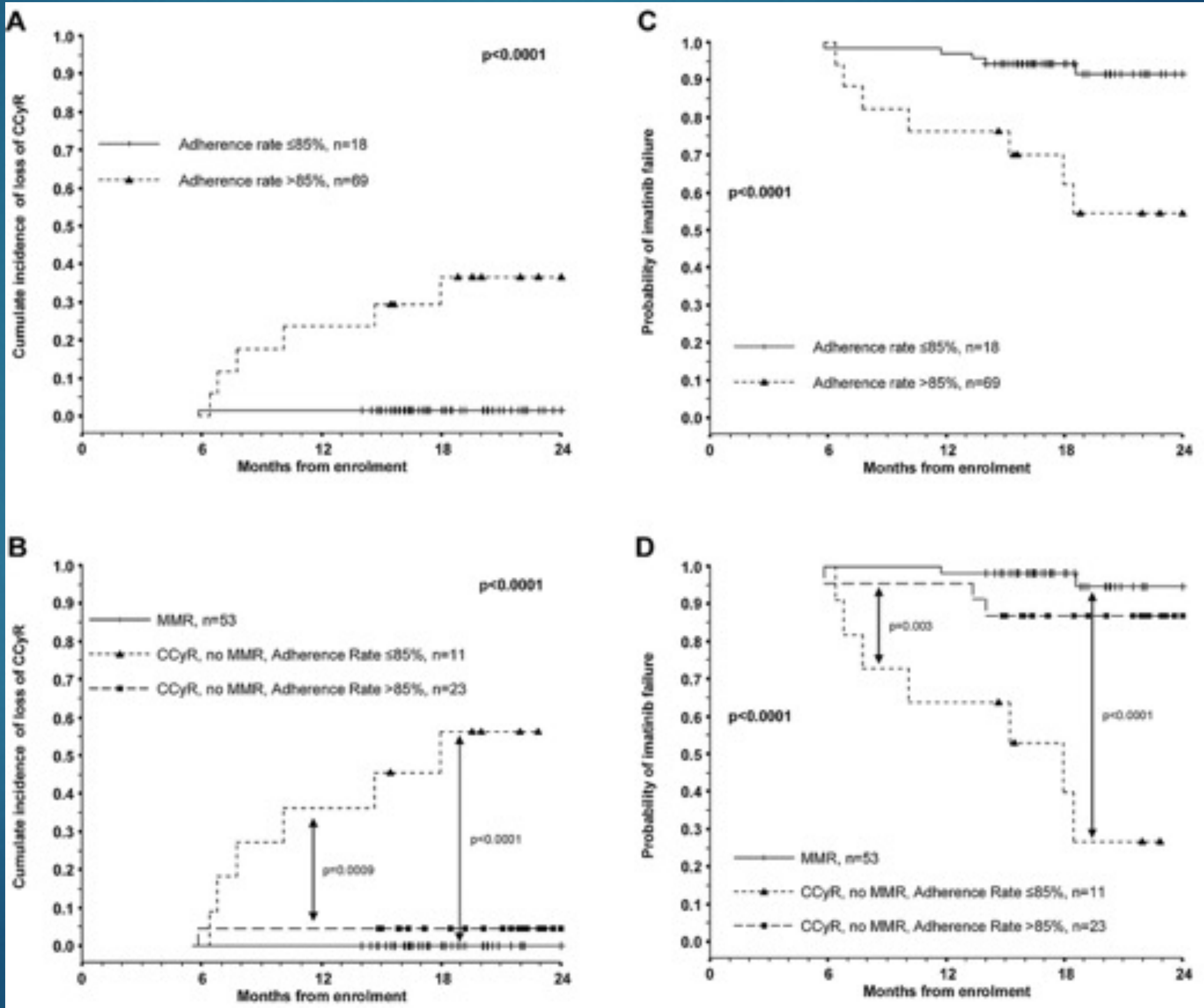
Viva la resistance

- Primary resistance(hematological criteria) in newly diagnosed CP-CML is rare:
  - 25% of patients do not obtain CCyR with imatinib
- Secondary Resistance more common:
  - Conformational changes in the binding site in BCR-ABL caused by point mutations
  - T315I is the mutations with the highest risk of resistance (gatekeeper mutation)
  - ID'ind the mutations may be helpful in selecting alternatives
- Consider mutational analysis for:
  - CP-CML with inadequate initial response
  - CP-CML with any loss of response
  - Progression

Compliance: pharmacy's role?

- Patient education on adherence/ monitoring of adherence is crucial
- ADAGIO trial: what does non-adherence do with imatinib?
  - Adherence < 85% had a higher probability of loosing CCyR at 2 years (27% v. 1.5%)
  - Only independent predictor for achieving a complete molecular response
- Preliminary data extrapolates to dasatinib and nilotinib

COMPLIANCE


A
p<0.0001
Cumulate incidence of loss of CCyR
Adherence rate ≤85%, n=18
Adherence rate >85%, n=69
Months from enrolment
C
p<0.0001
Probability of imatinib failure
Adherence rate ≤85%, n=18
Adherence rate >85%, n=69
Months from enrolment
B
p<0.0001
Cumulate incidence of loss of CCyR
MMR, n=53
CCyR, no MMR, Adherence Rate ≤85%, n=11
CCyR, no MMR, Adherence Rate >85%, n=23
p=0.0009
p<0.0001
Months from enrolment
D
p<0.0001
Probability of imatinib failure
p=0.003
p<0.0001
MMR, n=53
CCyR, no MMR, Adherence Rate ≤85%, n=11
CCyR, no MMR, Adherence Rate >85%, n=23
Months from enrolment

ACCELERATED PHASE

- Goal is to return to chronic phase
- Perform mutational analysis prior to switching therapy
- Accelerated Phase (AP-CML): All TKIs have shown to induce favorable responses
  - Imatinib 600 mg daily
  - Dasatinib 140 mg daily
  - Nilotinib 400 mg twice daily
  - Bosutinib 500 mg daily
- Note doses for 1st line are higher
- Can also use omacetaxine or alloHSCT

BLAST CRISIS

- High-dose induction chemotherapy used with response rates 25 – 60%
- Add a TKI to chemotherapy in BP-CML
  - Imatinib, dasatinib, nilotinib, bosutinib
- Recommendations:
  - Combination chemotherapy with TKI specific to AML or ALL

Message on Targeted Therapy

- Value in “me too,” drugs (drugs that multiple members are FDA-approved)
  - 5 CML TKI agents approved and they have defined roles in therapy
- Both similarities and differences between agents matter:
  - Does the difference provide an advantage in any way?
    - Toxicity profile (off-target effects)
    - Efficacy in treatment failure situations (place in therapy)
  - Does the similarity mean they are equivalent/interchangable?
    - Can information be extrapolated from one agent to the next?
- Changing the dosing strategies for different scenarios:
  - Dosing is may increase effect but also increase toxicity
  - Is this worth it?
- Compliance is an important consideration

Shifting Gears…Final Remarks…

User Toxicity/Survivorship

- Pharmacologically active agents that don't discern cancer cells from healthy cells
- Studies show that these agents increase the risk of cancer in healthcare workers
- Also effect outcomes of pregnancies:
  - Both men and women should heed caution while conceiving, pregnant or nursing
- In clinical practice, agents are prepared and handled in Biological Safety Class II Cabinets
  - Users wear gowns, gloves and in some cases respirators
- Please refer to OSH and NIOSH standards on safe handling practices
- Protect yourself and learn the rules!
- Gloves should be ASTM-tested against chemotherapy

One Last Toxicity…

- Large percentage of drug development is in oncology (~60%)
- Financial Toxicity is a big word these days..
  - Financial harm on patients caused by accepting costly therapies
- Consider the survival benefit/ cost relationship
  - Many agents cost several thousand for each cycle to add only a few months of overall survival benefit (at best)
- Consider imatinib cost $5,000 a month over 10 years ago
  - Now it costs $10,000 for the same drug and dosage form
  - Immunotherapies costing > $100,000 a year
  - Anti-nausea medications cost ~ $1,000 a cycle
- These costs are unsustainable for patients, hospitals and insurance companies

Something to Ponder…

Table 1. Proposed Financial Toxicity Grading Criteria

Grade	Description
1	Lifestyle modification (deferral of large purchases or reduced spending on vacation and leisure activities) because of medical expenditure
	Use of charity grants/fundraising/copayment program mechanisms to meet costs of care
2	Temporary loss of employment resulting from medical treatment
	Need to sell stocks/investments for medical expenditure
	Use of savings accounts, disability income, or retirement funds for medical expenditure
3	Need to mortgage/refinance home to pay medical bills
	Permanent loss of job as a result of medical treatment
	Current debts > household income
	Inability to pay for necessities such as food or utilities
4	Need to sell home to pay for medical bills
	Declaration of bankruptcy because of medical treatment
	Need to stop treatment because of financial burden
	Consideration of suicide because of financial burden of care

Any Questions?

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