Cancer is a complex disease caused by genetic and epigenetic mutations.

Simply stated, it is only unregulated cell division.

“Traditional” chemotherapy highjacks mechanisms of mitosis.

Understanding chemotherapy needs understanding of Biology 101.*

* Of course it gets complicated.

Merriam-Webster: Chemotherapy: noun: che • mio • thera • 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...

- Nitrogen Mustards were taboo and not used in battle, however
  - Ready to be used (feared Hitler would use when he was pushed)
  - Bomb raid on Bari, Italy on December 2nd, 1943
  - Sailors exposed had depletion of bone marrow stores and 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

World War II

- Nitrogen Mustards: Alkylation of guanine nucleotides in DNA causing inhibition of cell division and ultimately apoptosis
  - Showed promise however, responses to therapy was short 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
  - 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 to random mutations
- Cancer cells are no different from this
- Some are inherently resistant to a chemotherapy agent due to randomness alone

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 chemotherapy 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

- Competition growth
- Fraction of tumors progressing thru cell cycle influences susceptibility
- AKA growth fraction
- \( 10^7 \) Cells/ft Clinical Symptoms
- As time increases:
  - Cells develop resistance inherently
  - Competition over nutrients
  - Less cells going thru 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

- **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
- 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 huge 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
Pharmacodynamics

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

- \textbf{EC}_{50}
- \textbf{L}_{C50}

How much is sufficient?

At what cost does \textbf{E}_{\text{max}} come?

Kinetics/Genomics?

Drug Pathway Through The Body

- Highlights the overall complexity of the relationship of drug, effects and toxicities.
- Mastering these with \textbf{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
  - Example: Bevacizumab 5 mg/kg IV every 2 weeks

- Body Surface Area: Most common
  - \( \frac{\text{weight (kg)} \times \text{height (in)}}{3600} \)
  - Example: Cisplatin 75 mg/m\(^2\) IV every 3 weeks

- Others:
  - Calvert 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.

Review of Principles...

- The tales of the 1940's taught that disruption of cell cycle can affect 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?

- ROSES ARE GREY
- VIOLETS ARE GREY
Exploit the mechanisms

Cell Cycle and Chemotherapy

- 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

Regimens contain both types of agents

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)
  - Nitrosoureas (Carbazine)
  - Triazines (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
  - Hematologic 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 nucleophilic substances that bind and inactivate agents
  - Increased MMR and repair mechanisms

Mechlorethamine

N7 of guanine
Cyclophosphamide (Cytoxan)

- One of the most extensive agents used in therapy
- 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

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 1-10 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 and 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: Gastroesophageal reflux disease, 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
- 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
  - Oxaliplatin:
    - Peripheral Neuropathy
    - Myelosuppression: thrombocytopenia
S-Phase: Antimetabolites
FOLIC ACID ANALOGS, PYRIMIDINE ANALOGS, PURINE ANALOGS

Antifolates

- 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

Antifolates (Methotrexate)
Methotrexate MOA

- FH₂ is reduced by DHFR to FH⁴ (needed for purine synthesis)
- MTX blocks DHFR which inhibits FH⁴ polyglutamate (cytotoxic)
- Deoxyuridine monophosphate (dUMP) is converted to thymidine monophosphate (dTMP) (component of DNA)
- Leucovorin, an antidote can repel FH⁴ stores and continue cycle

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/m²/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
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 dihydropyrimidine dehydrogenase (DPD)
- Resistance:
  - Reduced conversion to active metabolite
  - Amplification of TS or alteration of TS binding site
  - Amplification of degradative enzymes

5-Fluorouracil in Practice

- Colon cancer: FOLFOX regimen (developed at RPCI):
  - Oxaliplatin 85 mg/m² IV on day 1
  - Leucovorin 400 mg/m² IV given with oxaliplatin on day 1, followed by
  - 5FU 400 mg/m² IV bolus, then
  - 5FU 2.4 g/m² IV given continuously over 46 hours
- Side effects:
  - Bolus: myelosuppression, angina
  - Continuous: N/V, diarrhea, mucositis, hand-foot syndrome
- Antidote: uridine triacetate

Natural Products

EPPODOPHYLLODIN, TAXANES, VINCA ALKALOIDS, CAMPTOTHECANS
Topoisomerase

- Type I Topoisomerase
  - Single Strand Break
  - Type IA
  - Type IB

- Type II Topoisomerase
  - Double Strand Break
  - Type IA
  - Type IB

Anthracycline: Doxorubicin

- Anthracyclines: 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)
  - Myelosuppression
  - Alopecia
  - Mucositis/N/V
  - Viscous
  - 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 (G2 Phase as well)
- Leads to apoptosis
- Side Effects:
  - Myelosuppression
  - Alopecia
  - Resistance:
  - P-gp overexpression
  - 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, α and β
- Microtubules grow from the spindle 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

Vinca alkaloids prevent microtubule assembly.

Taxanes: Polymerizing agents

- Discovered from Taxus brevifolia (Pacific Yew Tree)
- MOA: Inhibit depolymerization 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
  - 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:
  - Visceral
  - Neurotoxicity: Vincristine
  - Peripheral neuropathy
  - GI: constipation
  - Myelosuppression: Others
- Resistance:
  - P-gp up-regulation
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
  - Myelosuppression
  - H: Doxorubicin: Topoisomerase II inhibitor (S-phase)
  - Cardiotoxicity, NV, myelosuppression, mucositis
  - 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 inhibition of the ATP-binding domain
  - May also target other downstream enzymes active in signal transduction
    - RAS
    - RAF
4 Key Issues (Pearls)

- 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 affect 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 T3, p210 that regulates proliferation
  - BCR-ABL is a TK that is cytokine independent on signal
  - Thus there 95% of time
CML Phases

- Chronic Phase (3-5 years)
  - Asymptomatic

- Accelerated Phase (months)
  - Blast 10 – 19%
  - Platelets < 50,000 or > 1,000,000
  - Clonal evolution: extra abnormalities accumulate
  - Non-specific symptoms: fatigue, night sweats, fever

- Blast Crisis (< 1 year)
  - Blast > 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, PDGFR (Multikinase)
- Side effects:
  - Edema, rash, nausea, myalgias
  - Myelosuppression, hepatotoxicity
- Resistance:
  - BCR-ABL kinase binding domain mutations
  - Overamplification

Imatinib

- Alteration of binding site
TKI Class side effects

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Management Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathy</td>
<td>Hold until recovery, potential dose reduction</td>
</tr>
<tr>
<td>Anemia</td>
<td>Do not support in patients with renal insufficiencies.</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Hold until recovery, potential dose reduction</td>
</tr>
<tr>
<td>Rash</td>
<td>Topical or systemic steroids:</td>
</tr>
<tr>
<td></td>
<td>Dose reduction, interruption or discontinuation</td>
</tr>
</tbody>
</table>

**Dasatinib (Sprycel)**

- 2nd generation BCR-ABL inhibitor; 325 times more potent than 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 BGC 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 GNE: imatinib, dasatinib, nilotinib, considering:
  - Toxicities
  - Age or ability to tolerate therapy
  - Comorbid conditions
  - Risk
  - 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

- 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

T315I CML and Ponatinib

- 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, FGFR, PDGFR, EPHA, SRC, KIT, RET, EGFR, FL3
  - Side effects:
    - Oral dose:
    - 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 mutation 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 losing CCyR at 2 years (27% v. 1.5%)
  - Only independent predictor for achieving a complete molecular response
- Preliminary data extrapolates to dasatinib and nilotinib

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 400 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 alloHCT
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 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)
- Changes in the dosing strategies for different scenarios:
  - Does it increase effect but also increase toxicity?
  - Is it worth it?
- Compliance is an important consideration
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 affect outcomes of pregnancies.
- Both men and women should treat cancer 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 OSHA 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>
<thead>
<tr>
<th>Table 1</th>
<th>Pre-Post Financial Toxicity Scoring Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td>Description</td>
</tr>
<tr>
<td>1</td>
<td>Lifespan modification of lifestyle, time lost, income reduced</td>
</tr>
<tr>
<td></td>
<td>Use of savings, unemployment, and reduction in income</td>
</tr>
<tr>
<td>2</td>
<td>Temporary loss of employment due to medical treatment</td>
</tr>
<tr>
<td></td>
<td>Use of savings, disability income or retirement funds</td>
</tr>
<tr>
<td>3</td>
<td>Need to sell/mortgage home to pay medical expenses</td>
</tr>
<tr>
<td></td>
<td>Permanent loss of job due to medical treatment</td>
</tr>
<tr>
<td>4</td>
<td>Death of a household income provider</td>
</tr>
<tr>
<td></td>
<td>Death of an income provider due to medical treatment</td>
</tr>
</tbody>
</table>

- Financial burden due to medical treatment.
- Needs to avoid treatment because of financial burden.
Any Questions?

References