# Pharmacokinetics of Oncology Drugs

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## Learning Objectives

- Understand the importance of pharmacokinetics with the use of oncology drugs  
- Monitor pharmacokinetic (PK) parameters with the use of oncology drugs  
- Manage abnormal pharmacokinetics parameters with the use of oncology drugs

## Definition of Pharmacokinetics

- "The quantitative analysis of the process of drug absorption, distribution, and elimination that determine the time course of drug action"  
- "What the body does to the drug"  
- ADME:  
  - Absorption  
  - Distribution  
  - Metabolism  
  - Excretion


## Importance of Pharmacokinetics

- The clinical importance of PK (and PD) is based on the principle that concentration-response relationships are less variable than dose-response relationships for any specific drug  
- Understanding interpatient variability in drug PK allows us to implement strategies to reduce variability and hopefully achieve more consistent clinical outcomes and maximize patient benefit

## Factors than can affect PK

- Kidney function  
- Hepatic function  
- Age  
- Body surface area (BSA)  
- Concomitant medications  
- Pharmacogenetic polymorphisms in drug-metabolizing enzymes

## Additional factors that may alter PK in cancer patients

- Prior gastrointestinal surgery (if oral administration)  
- Poor nutritional status  
  - Hypoalbuminemia  
- Polypharmacy  
- Advanced age  
- Altered renal or hepatic function
## Effects of Altered Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Effect on Serum Concentration</th>
</tr>
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<tbody>
<tr>
<td>Altered absorption</td>
<td>Increased or decreased</td>
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<tr>
<td>Displacement from plasma</td>
<td>Increased</td>
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<tr>
<td>protein binding sites</td>
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<tr>
<td>Inhibition of metabolism</td>
<td>Increased</td>
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<tr>
<td>Induction of metabolism</td>
<td>Decreased</td>
</tr>
<tr>
<td>Altered renal excretion</td>
<td>Increased or decreased</td>
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</tbody>
</table>

## Absorption

- Historically, most chemotherapy agents have been given intravenously
- In recent years the use of oral agents has grown and will continue to do so
- The PK parameter most closely associated with oral absorption is bioavailability (F)

## Distribution

- The volume of distribution (Vd) relates to the amount of drug in the body to the concentration observed in the measured compartment
- Represents a constant of proportionality
- The rate and extent to which a drug distributes into tissues depends on many factors
- Drug lipophilicity
- Tissue permeability
- Tissue-binding constants
- Local organ blood flow

## Metabolism

- Hepatic CYP system is the main site of drug metabolism for many oncology agents
- Many are cleared by the CYP3A4 system in the liver, although biotransformation can occur in the gut, lung, kidneys, blood and tumors
- Traditionally, drug-metabolizing processes have been divided into phase I and phase II reactions
- Typically generate more polar, biologically inactive metabolites
- CYPP450 system is the best characterized family of phase I drug-metabolizing enzymes

## Absorption

- Oral bioavailability can be altered in cancer patients due to changes in the integrity of the gastrointestinal tract caused by chemotherapy side effects, surgery, radiation or nausea/vomiting

## Distribution

- Chemotherapy agents can bind to several blood components
  - Albumin
  - Alpha 1 acid glycoprotein
  - Lipoproteins
  - Immunoglobulins
  - Erythrocytes
- Drug displacement from blood components or tissue-binding sites increases the apparent distribution volume
- Therapeutic implications of this have yet to be defined
Altered Metabolism - Cytochrome P450 system

- The Cytochrome (CYP) P450 system was discovered in the 1960’s when mouse hepatic microsomal cells were stained with pigment
- Pigment produced an unusual absorption “peak” at 450 nm on spectroscopy
- Hence
  - Cell = cyto
  - Color = chrome
  - Pigment = P
  - At 450 nm = 450

CYP’s are a superfamily of oxidases with nomenclature driven by location of corresponding gene on human genome

- Terminology
  - CYP = cytochrome P450
  - Number = gene family
  - Letter = gene subfamily
  - Number = individual gene
  - Example = CYP 3A4
- Known CYP’s: CYP 3A4/5, 2D6, 1A2, 2C9, 2C19, 2B6, 2A6, 2C8, 2E1

Characteristics of P450 subfamilies involved in drug metabolism:
- All are oxidases
- Polymorphisms exist commonly
- Varying amounts of an enzyme between populations in a species (ex. Asians vs. caucasians)
- All have specific substrates
  - Ex. Tamoxifen is oxidized by a CYP 2D enzyme, not a CYP 3A enzyme
  - Substrate redundancy between families

Impact of hepatic dysfunction on liver drug-metabolizing pathways can be difficult to assess
- Liver dysfunction can affect glucuronidation
- Cirrhosis can reduce drug-metabolizing capacity by 30-50%
- Malnutrition may also alter the hepatic clearance of drug

Certain chemotherapy agents are primarily cleared by the kidneys
- These agents, if not adjusted for impaired renal function can cause increased toxicity due to decreased drug elimination
Alkylating Agents

- Nitrogen mustards
  - Cyclophosphamide
    - 5-25% of drug excreted unchanged in the urine
      - In renal insufficiency, measurable changes in PK parameters have been demonstrated
      - GFR between 10-50 ml/min: Give 75% of usual dose
      - GFR < 10 ml/min: Give 50% of usual dose
    - Parent drug undergoes hepatic biotransformation (CYPs 2B6, 2C9, 3A4) to its active form
      - Bilirubin between 3-5 mg/dl: Reduce dose by 25%
      - Bilirubin > 5 mg/dl: Omit

- Monitoring
  - Baseline CBC (prior to therapy, at expected nadir, prior to next cycle or as appropriate)
  - Regular urinalysis for red blood cells which may precede hemorrhagic cystitis (especially important in patients with potentially altered excretion)

Alkylating Agents

- Nitrogen Mustards
  - Cyclophosphamide
    - Monitoring
      - CNS symptoms (somnolence, hallucinations and coma reported especially with altered clearance)
      - Urinalysis prior to each dose (hold therapy if hematuria noted)
      - Electrolytes (especially potassium for hypokalemia)
      - CBC at baseline and prior to each dose

Alkylating Agents

- Nitrogen mustards
  - Ifosfamide
    - 3-56% of parent drug excreted unchanged in the urine depending upon dose used
      - GFR between 10-50 ml/min: Decrease dose by 25%
      - GFR < 10 ml/min: Decrease dose by 50%
    - Like cyclophosphamide, must be activated via the CYP system to its active, cytotoxic component (4-hydroxy-ifosfamide)
    - Recommendations in any degree of hepatic failure are not available

Alkylating Agents

- Nitrogen mustards
  - Ifosfamide
    - Monitoring
      - CNS symptoms (somnolence, hallucinations and coma reported especially with altered clearance)
      - Urinalysis prior to each dose (hold therapy if hematuria noted)
      - Electrolytes (especially potassium for hypokalemia)
      - CBC at baseline and prior to each dose

Alkylating Agents

- Nitrosoureas
  - Carmustine
    - Rapidly degraded after given IV with no detectable drug noted after 15 minutes
    - 60-70% of total dose is excreted in the urine within 96 hours
    - No dosage adjustment suggested in renal impairment
    - Cytotoxic activity is likely due to metabolites, however metabolic pathways are not understood
    - No dosage adjustment recommended in hepatic impairment

- Monitoring
  - CBC (delayed bone marrow suppression)
  - Pulmonary function tests (pulmonary fibrosis and infiltrates reported with long term use and/or high doses)
  - LFT’s – hepatotoxicity usually reversible
### Alkylating Agents

**Alkyl sulfonates**
- **Busulfan**
  - When given PO, absorption varies widely
  - Renal excretion is minimal
  - No dosage adjustment necessary in renal impairment
  - Predominantly metabolized by conjugation with glutathione which undergoes further oxidative processes in the liver
  - No suggestions for adjustment in hepatic impairment
  - Of note – use of busulfan with phenytoin results in decreased plasma concentrations of busulfan of up to 15%.

### Alkylating Agents

**Triazenes**
- **Temozolomide (Temodar)**
  - Excellent bioavailability
  - Not studied in patients with mucositis or other alterations in GI mucosa
  - Spontaneously hydrolyzed in plasma to active components
  - No appreciable metabolism in the liver
  - Renal excretion is approximately 40%
  - Manufacturer advises to use caution in severe renal and hepatic impairment
  - Monitoring of CBC, liver function and CNS status recommended.

### Alkylating Agents

**Platinum analogues**
- **Cisplatin**
  - Protein binding: 90%
  - Likely not clinically significant in hypoalbuminemia
  - Probably metabolized by non-enzymatic pathways to inactive metabolites
  - No adjustment in hepatic dysfunction
  - Renal excretion: Up to 45%
  - Usually try to avoid in renal impairment but can be used if necessary
  - GFR 10-50 ml/min: 75% of usual dose
  - GFR < 10 ml/min: 50% of usual dose

### Alkylating Agents

**Platinum analogues**
- **Carboplatin**
  - Renal and total body clearance of carboplatin are reduced in renal impairment
  - Dose adjustments are necessary to avoid severe bone marrow toxicity
  - Calvert equation: Dose (mg) = Target (AUC) X (GFR + 25)
  - No dose alterations necessary in hepatic impairment
  - Monitoring
    - Mainly CBC with platelets once or twice between courses of therapy (in renal dysfunction a higher incidence of severe myelosuppression is seen)
**Alkylating Agents**

- **Platinum analogues**
  - **Oxaliplatin**
    - 70-95% protein bound
    - Primarily excreted via the kidneys, however no good in vivo data to offer dosing adjustments in renal impairment
    - In patients > 65 years of age, increased toxicity was seen
    - Rapidly metabolized in plasma (non-P450 mediated)
    - No dosage adjustment necessary in hepatic impairment
  - **Monitoring**
    - CBC prior to each chemotherapy cycle
    - Neurologic exam prior to each treatment course (acute and persistent peripheral neuropathy very common and exacerbated by cold)

**Enzyme Inhibitors**

**Anthracyclines**
- **Daunorubicin**
- **Doxorubicin**
- **Idarubicin**
- **Epirubicin**
  - Protein binding among agents varies
  - All are extensively metabolized by the P450 system (3A) and other tissues to active metabolites
  - Dose reductions absolutely necessary in hepatic impairment to avoid life-threatening toxicity
  - Renal excretion varies

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**Enzyme Inhibitors**

**Anthracyclines**

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**Enzyme Inhibitors**

**Epipodophyllotoxins**
- **Etoposide**
  - Absorption of oral etoposide varies widely; at high doses, bioavailability decreases
  - Highly protein bound
  - Known alterations in protein binding with low serum albumin
  - Clinical significance of this not known
  - Extensively metabolized via the liver
  - Dose modifications in hepatic impairment
    - Bilirubin 1.5-3.0 mg/dL: Decrease by 50%
    - Bilirubin > 3.1 mg/dL: Do not use
  - Monitoring
    - LFT’s: Especially with high dose therapy or in patients with altered elimination
    - CBC during therapy

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**Enzyme Inhibitors**

**Epipodophyllotoxins**
- **Etoposide**
  - 40% of dose is excreted unchanged in urine
  - Dosage adjustments in renal impairment suggested
    - CrCl between 15-50 mL/min: Decrease dose by 25%
    - CrCl < 10 mL/min: Decrease dose by 50%
  - Monitoring
    - CBC during therapy

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  - Monitoring
    - CBC during therapy
Topoisomerase I inhibitors

- Camptothecins
- Irinotecan
  - Metabolized mainly in liver by carboxylesterase enzymes to highly active metabolite SN-38
  - SN-38 then conjugated to form a glucuronide metabolite by enzyme UDP-glucuronosyl transferase 1A1 (UGT1A1)
  - Genetic polymorphisms exist in this enzyme leading to reduced activity
  - 10% of the North American population has this homozygous allele
  - Can cause up to a four-fold risk of severe toxicity
  - Dosage reductions suggested, but no clear guidelines exist

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Topoisomerase Inhibitors

- Camptothecins
  - Irinotecan
    - In hepatic dysfunction
      - Higher AUC's noted, but no formal dose adjustments have been made
    - No dosage adjustment for renal insufficiency
    - Monitoring
      - Vital signs during and after infusion
      - Diarrhea (late onset): Monitor closely in elderly and in patients with impaired organ function
      - CBC: Frequently with suspected genetic polymorphism

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Antimicrotubules

- Vinca Alkaloids
  - Vincristine
  - Vinblastine
  - Vinorelbine
    - All are extensively metabolized via the CYP 3A subfamily
    - Dosage adjustments necessary in hepatic impairment
      - Bilirubin 1.5-3.0 mg/dL: Decrease dose by 50%
      - Bilirubin > 3.1: Do not use
    - Minimal renal excretion
    - No dosage adjustment recommended in renal impairment

- Vincristine
  - Frequent monitoring for neurologic toxicity (paralytic ileus, paresthesia, numbness, sensory loss, loss of deep tendon reflexes) – toxicity is cumulative

- Vinblastine and vinorelbine
  - CBC with platelets
    - Neurologic toxicity MUCH less common than with vincristine

Antimicrotubules

- Taxanes
  - Paclitaxel
    - Highly protein bound (up to 98%)
    - Likely not clinically significant based upon available data
    - Extensively metabolized via the CYP 3A subfamily
      - Dose adjustments necessary in hepatic insufficiency
      - No dosage adjustment in renal insufficiency
  - Guidelines based on standard 3 hour infusion

- Bilirubin
  - Transaminase levels
    | Transaminase levels | Bilirubin | Recommended Dose |
    |---------------------|----------|-----------------|
    | < 10X ULN AND       | < or = 1.25 ULN | 175 mg/m2 |
    | < 10X ULN AND       | 1.26-2X ULN  | 135 mg/m2 |
    | < 10X ULN AND       | 2.01-5X ULN  | 90 mg/m2 |
    | > or = 10X ULN OR   | >5X ULN     | Do not use     |
### Antimicrotubules

- **Taxanes**
  - **Docetaxel**
    - Highly protein bound to various plasma proteins
    - Primarily metabolized in the liver via CYP 3A4 to active and inactive metabolites
    - Metabolic pathways not clearly elucidated
    - Dosage adjustment likely necessary in hepatic insufficiency although minimal guidelines exist
    - AST or ALT > ULN AND Alk Phos > 2.5 ULN: Do not give

- **Monitoring**
  - **Paclitaxel**
    - CBC with platelets
    - Peripheral neuropathy (increased risk with higher doses and total cumulative dose)
    - Musculoskeletal (arthralgia/myalgia) – increased risk with higher cumulative doses
  - **Docetaxel**
    - Edema – severe edema occurs more commonly in patients with elevated LFT’s
    - Nail changes – severe changes more common with elevated LFT’s
    - Mucositis
    - CBC with platelets – anemia, neutropenia and thrombocytopenia more severe with elevated LFT’s

### Antimetabolites

- **Folate antagonists**
  - **Methotrexate**
    - Bioavailability varies widely (17-90%) depending upon dose given
    - Higher doses (40 mg/m²) are less well absorbed
    - Metabolism in via the liver and intracellular
    - Not well described; however dose adjustment suggested in hepatic impairment
    - Bilirubin > 3.0 mg/dL and AST < 180 IU: Give full dose
    - Bilirubin 3.1-5.0 mg/dL and AST > 180 IU: Give 75% of dose
    - Bilirubin > 5.0 mg/dL: Do not use

- **Monitoring**
  - **Serum methotrexate levels**
  - **Urine pH** (should be > 6.5 to facilitate excretion)
  - **Serum Cr and BUN daily**
  - **CBC with platlets** (bone marrow suppression may be more severe in patients with impaired renal function)

### Antimetabolites

- **Purine analogs**
  - **Mercaptopurine**
    - Bioavailability ranges from 5-37%
    - Extensively metabolized after oral administration via intestinal and first-pass hepatic metabolism by two major pathways
    - In individuals with inherited deficiency of thiopurine methyltransferase (TMPT), the enzyme responsible for catabolism of mercaptopurine the dose should be decreased by 90% to avoid life-threatening toxicity
    - May need lower doses in renal and hepatic insufficiency, however no dosage guidelines exist
    - **Monitoring**
      - Weekly CBC with platelets
      - LFT’s weekly when starting therapy; if baseline hepatic impairment – monitor more frequently

### Antimetabolites

- **Pyrimidine analogues**
  - **Cytarabine**
    - Converted intracellular to active drug
    - Extensively metabolized in the liver to inactive metabolite(s)
    - Reduce dose in liver impairment; no guidelines available
    - Approximately 80% (mainly metabolite) is excreted in the urine
    - Risk of toxicity (mainly neurologic) is directly related to renal function throughout therapy and dose adjustments are necessary (if CrCl < 60 ml/min)
**Antimetabolites**

- Pyrimidine analogues
  - Cytarabine
  - Dosage adjustments in renal impairment
    - Dose decrease
    - Once instead of twice daily dosing
  - Monitoring
    - CBC with platelets
    - LFT’s (high-dose therapy)
    - Renal function

<table>
<thead>
<tr>
<th>Serum Creatinine</th>
<th>Recommended Cytarabine Dose (High-dose therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.5 mg/dL</td>
<td>2-3 g/m²</td>
</tr>
<tr>
<td>1.5-1.9 mg/dL or ↑ from baseline by 0.5-1.2 mg/dL</td>
<td>1 g/m²</td>
</tr>
<tr>
<td>&gt; or = 2.0 mg/dL or ↑ in Cr &gt; 1.2 mg/dL</td>
<td>0.1 g/m²</td>
</tr>
</tbody>
</table>

**Antimetabolites**

- Pyrimidine analogs
  - Gemcitabine
    - Negligible protein binding
    - Phosphorylated intracellularly to active drug
    - Deaminated in liver and kidney to inactive metabolite
      - "Caution" recommended in renal and hepatic insufficiency, however no guidelines offered
    - In elderly, clearance is noted to be slower
    - Monitoring
      - Hematologic (mainly neutropenia), renal function

- Fluorouracil (5-FU)
  - Complex metabolism to active and inactive metabolites
  - 1-3% of population has deficiency in the enzyme dihydropteroate synthetase (DPS) which is partly responsible for catabolic pathway of 5-FU
  - Experience severe toxicity when given 5-FU
  - If bilirubin > 5.0 mg/dl: Alternative agent is recommended
  - Monitoring
    - CBC and platelets prior to each dose
    - LFT’s
    - GI

**Antimetabolites**

- Pyrimidine analogues
  - Capecitabine
    - Pro-drug of 5-FU: Crosses GI mucosal barrier unchanged; bioavailability information lacking
    - Converted to active form via liver and in tumor tissues
    - Active and inactive metabolites almost exclusively excreted renally
      - Dosing adjustments in renal impairment
        - CrCl > 30-50 ml/min: Dose reduce by 25%
        - CrCl < 30 ml/min: Contraindicated

**Targeted Therapies**

- Monoclonal Antibodies
  - Gemtuzumab
  - Alemtuzumab
  - Rituximab
  - Trastuzumab
  - Cetuximab
  - Panitumumab
  - As a general rule, these agents do not require any dosage adjustment based on altered PK parameters as they are not metabolized and elimination does not correlate with kidney function
### Targeted Therapies

**Tyrosine kinase inhibitors**

- **Erlotinib (Tarceva)**
  - Bioavailability of 60% after oral administration
  - Primary route of clearance is hepatic metabolism via CYP 3A4 (minor 1A2) and biliary excretion
  - In hepatic impairment (no lab parameters specified), dose reductions in increments of 50 mg may be required
  - Clinical studies demonstrated no differences in PK between older and younger populations
  - Renal excretion is minimal
  - Monitoring parameters: LFT’s, PT/INR, renal function

- **Imatinib (Gleevec)**
  - Bioavailability of 98% after oral administration
  - Highly protein bound to albumin and alpha-1 acid glycoprotein
  - Likely not clinically significant
  - Extensively metabolized in the liver via CYP 3A4 to an active metabolite (and some minor inactive metabolites)
  - Eliminated predominantly in feces, mainly as metabolites
  - Minimal renal excretion

- **Sunitinib (Sutent)**
  - Bioavailability does not seem to be altered in the oncology population
  - 95% protein bound
  - Extensively metabolized via CYP3A4 in the liver to a primary active metabolite
  - Renal excretion: 13%
  - Dosage adjustment in hepatic insufficiency
  - No adjustment needed in Child-Pugh Class A or B
  - Not studied in Child-Pugh Class C

- **Lapatanib (Tykerb)**
  - Bioavailability is incomplete and variable
  - Highly protein bound (>99%) to albumin and alpha-1 acid glycoprotein
  - Extensive metabolism in the liver via CYP 3A4 and 3A5; additional minor metabolism occurs via 2C19 and 2C8 to oxidated metabolites
  - Mainly eliminated via fecal excretion
  - Minimal renal excretion
  - Dosing adjustments necessary in hepatic impairment
  - 750 mg/day in Child-Pugh Class C (usual dose is 1250 mg/day)
Targeted Therapies

- Tyrosine kinase inhibitors
  - Lapatinib
    - Monitoring
    - Magnesium and potassium; EKG (prolonged QT has been reported)
    - Hepatic function
    - Pulmonary function (interstitial lung disease and pneumonitis)
    - Left ventricular ejection fraction (baseline and every 8 weeks)

- Sorafenib (Nexavar)
  - Bioavailability: 38-49% on empty stomach
  - 99.5% protein bound
  - Extensive metabolism in the liver via CYP3A4 and glucuronidation to highly active metabolite and some minor metabolites
  - Major route of excretion: Feces
    - In hepatic impairment (Child Pugh Class A and B with hepatocellular carcinoma) dosage adjustment is not recommended, but close monitoring should be performed
    - Child Pugh Class C: Has not been studied

- Minimal renal excretion
  - No dosage adjustment necessary in renal impairment
  - In elderly (> 65 yrs) no dosage adjustment is necessary

- Monitoring
  - Blood pressure (hypertension): weekly for first six weeks, then periodically
  - Cardiac ischemia (may be higher in patients with hepatocellular carcinoma)
  - Hand-foot syndrome
  - Amylase and Lipase levels
  - CBC if indicated

Miscellaneous Agents

- Bortezomib (Velcade)
  - Not highly protein bound
  - Primarily metabolized in the liver via CYP 450 3A4, 2D6, 2C19, 2C9 and 1A2 to multiple metabolites
  - Extent of renal and other excretion unknown in humans
    - Dose adjustment in renal impairment is not necessary
    - Dose adjustment in hepatic impairment may be necessary as clearance may be decreased

- Monitoring
  - Frequent monitoring of CBC and platelets
  - Peripheral neuropathy
  - Cardiopulmonary symptoms

- Bleomycin
  - Extent of protein binding unknown
  - Metabolized primarily by the liver to at least one active metabolite
  - Approximately 50% renal excretion
    - Dosage adjustments in renal insufficiency necessary
    - Multiple guidelines exist

<table>
<thead>
<tr>
<th>Serum creatinine</th>
<th>% of full dose</th>
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<tr>
<td>2.5-4.0 mg/dL</td>
<td>25%</td>
</tr>
<tr>
<td>4.1-6.0 mg/dL</td>
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</tr>
<tr>
<td>6.0-10 mg/dL</td>
<td>10%</td>
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</table>
Miscellaneous Agents

- Bleomycin
  - Monitoring
    - Mainly pulmonary function tests
    - Pre-therapy; every two months or at first sign of possible pulmonary toxicity

Miscellaneous Agents

- Thalidomide
  - Bioavailability not determined in humans
  - High protein binding (exact extent unknown)
  - Appears to go non-enzymatic hydrolysis in the plasma, however exact metabolism is not known
  - Minimal renal excretion
    - Dosage alteration in renal or hepatic impairment is not necessary
  - Monitoring: Thrombotic events, skin reactions, routine neurologic evaluations

Summary

- Stay current
- Have thorough and up to date references readily available at your practice site
  - Use list-serves
- Apply appropriate clinical judgement and monitoring when dosing chemotherapy in patients with known altered PK parameters

Questions