Oral Anticancer Therapy

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Learning objective

- Outline how oral chemotherapy is different from parenteral chemotherapy
- Recognize the common misperceptions about oral chemotherapy and discuss these with patients
- Utilize patient selection criteria for oral CMT regimens
- Discuss the strategy to improve adherence on oral anticancer therapy
Progress in the medical tx of cancer

Early cancer
Surgery/Cauterization
3000-1600 BC

Radiation
“Cure” reported
1899

Monoclonal Ab
Mid-1970s

Chlorambucil
1984

Cytotoxic CMT
1940s

Cyclophosphamide
tab.
1959

IFN-α, IL-2
1980s

Mercaptourine
1953

Temozolamide
1999

Imatinib
2001

Lapatinib
2007

CMT

Gefitinib
2002

Pazopanib
2009

Everolimus
2009

Ongoing Research
directed of targeting
specific mechanism
2013

Imatinib
2001

Sorafenib
2005

Sunitinib
2006

Crizotinib
Regorafenib
Vemurafenib
2012

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Lapatinib
2007

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Cyclophosphamide
tab.
Introduction

- Oral chemotherapeutic drugs have been available for decades
  - Conventional Anticancer Oral Therapy (AOT)
    - Chlorambucil
    - Cyclophosphamide
    - Methotrexate
    - 6-mercaptopo-purine (6-MP)
Drivers of Oral chemotherapy

- In the past, developers of new anti-cancer therapies focused primarily on parenteral drug delivery
- This route bypassed the variable absorption patterns of the GI tract.
Drivers of Oral chemotherapy

- In the past, (cont.)
  - Oral drugs must be stable in the low pH environment of stomach
  - Oral drugs must dissolve in the small intestine where the drug is absorbed
  - Interaction with other substances in the GI, such as food or other drugs
  - First pass effect on the liver
Drivers of Oral chemotherapy

- Oral chemotherapy is changing model of therapy

Targeted therapy
What are Targeted therapies?

- Therapies directed towards a specific target on cells that affects angiogenesis and cell cycle mechanisms
- Main targets:
  - Cell specific markers
  - EGFR-Epidermal Growth factor Receptor
  - VEGF-Vascular Endothelial Growth Factor
- Therapies:
  - Monoclonal Antibodies
  - Tyrosine Kinase Inhibitors
Proliferation
HER Family: Receptors and Ligands
Naming of targeted agents: Monoclonal Antibodies

- First syllable – Unique name
- Second syllable – Target
  - tu = tumor
  - li = immune system
  - vi = virus
  - ci = circulatory system
  - os = bone
- Third syllable – Source
  - o = mouse
  - zu = humanized
  - e = hamster
  - a = rat
- Last syllable – mab
QUESTION

Which of the following monoclonal antibodies would be expected to cause the lowest incidence of human-antimouse antibodies (HAMA) reactions?

A. Epratuzumab  
B. Cetuximab  
C. Bevacizumab  
D. Panitumumab  
E. Tositumomab
Naming of targeted agents: Protein targets

- First syllables – Unique name
- Middle syllable – Target
  - anib (angiogenesis)  pazopanib
  - farnib (farnesyl transferase)  tipifarnib
  - rafenib (raf kinase)  sorafenib
  - tinib (tyrosine kinase)  imatinib
- Last syllable – ib (inhibitor)
Oral Anticancer therapy

Oral CMT
- Capecitabine
- Cyclophosphamide
- Temozolamide

Oral TKI
- Gefitinib
- Erlotinib
- Lapatinib
- Sunitinib
- Sorafenib
Administration

Dose & Dose adjustment

Miss dose

ADR

Stability

Prevention and management ADR

Special administration

Drug – Drug & Drug - Food interaction

ADR
Oral Chemotherapy
## Pharmacokinetic: Absorption & Solubility

<table>
<thead>
<tr>
<th>Drug</th>
<th>Absorption (bioavailability)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>• &gt;75%</td>
</tr>
<tr>
<td></td>
<td>• Food don’t have affect</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>• Readily absorp</td>
</tr>
<tr>
<td></td>
<td>• effect of food reduce the rate and extent absorption</td>
</tr>
<tr>
<td>Temozolamide</td>
<td>• Rapid and complete</td>
</tr>
<tr>
<td></td>
<td>• To reduce nausea; take on empty stomach or bedtime</td>
</tr>
</tbody>
</table>
## Dosage and administration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>ac</th>
<th>pc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide (25 mg/tab)</td>
<td>100 mg/m²/day on D1-14 on 21 day cycle</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Capecitabine (150, 500 mg)</td>
<td>Breast cancer: 1250 mg/m² bid on D1-14 on 21 day cycle</td>
<td>❌</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Colon cancer: 1000 mg/m² bid on D1-14 on 21 day cycle</td>
<td></td>
<td>(within 30 min After meal)</td>
</tr>
<tr>
<td>Temozolamide (20,100 mg)</td>
<td>• 75 mg/m² OD CCRT followed by 150-200 mg/m² OD on D1-5 days q 28 days</td>
<td>✓</td>
<td>❌</td>
</tr>
</tbody>
</table>
## Dose Adjustment

<table>
<thead>
<tr>
<th></th>
<th>Renal impairment</th>
<th>Hemodialysis patient*</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>✗ (yes for high dose)</td>
<td>• ↓25%</td>
<td>✗</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Give after HD</td>
<td></td>
</tr>
<tr>
<td>Capecitabine</td>
<td>• Clcr 30-50 ml/min: ↓25%</td>
<td>No data</td>
<td>• Mild-moderate: ✗</td>
</tr>
<tr>
<td></td>
<td>• Clcr &lt; 30 ml/min: do not use</td>
<td>Should be avoid in HD pt</td>
<td>• In severe hepatic: have not been studied</td>
</tr>
<tr>
<td>Temozolamide</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
</tbody>
</table>

*use with extreme caution

†For dialysis depend on which dialysis machine they use

¥For dialysis depend on which dialysis machine they use
<table>
<thead>
<tr>
<th>Drug</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>Hepatic to active metabolite Substrate of CYP2B6 (major)</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>• Hepatic: extensively metabolized enzymatically</td>
</tr>
<tr>
<td></td>
<td>• Inhibit CYP2C9 (strong)</td>
</tr>
<tr>
<td>Temozolamide</td>
<td>Spontaneously hydrolyzed at physiological pH to active species, MTIC (Dacarbazine)</td>
</tr>
</tbody>
</table>
## Drug interaction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>CYP 2B6 inh. (mod.): allopurinol CYP 2B6 inh. (strong): Denosumab, Etanercept</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>CYP2C9 substrate: Phenytoin, carvedilol, leflunomide</td>
</tr>
<tr>
<td>Temozolamide</td>
<td>No</td>
</tr>
</tbody>
</table>
Avoid crushing tablets

Use the injection to prepare an oral solution

should be undertaken in appropriate facilities
## Special medication by NG-tube

<table>
<thead>
<tr>
<th>Medication</th>
<th>Preparation</th>
</tr>
</thead>
</table>
| Cyclophosphamide      | • Extemporaneous liquid preparations for oral administration may be prepared by dissolving tablets in aromatic, Elixir.  
                        | • Preparations should be stored under refrigeration in glass containers and used within 14 days |
| Capecitabine          | Fill the cup with 200 ml of water and add the correct number of Capecitabine tablets. Leave the tablets in the liquid to dissolve. This may take about 15 minutes |
| Temozolamide          | mixing Temozolamide capsule with apple juice in chemo hood. [stability =120 minutes when mixed with apple juice or applesauce] |
Intragastric administration: cyclophosphamide

- Stop the enteral feed.
- Flush the enteral feeding tube with the recommended volume of water.
- Draw the medication solution into an appropriate size and type of syringe.
- Flush the medication dose down the feeding tube.
- Draw an equal volume of water into the syringe and also flush this via the feeding tube (this will rinse the syringe and ensure that the total dose is administered).
- Finally, flush with the recommended volume of water.
- Re-start the feed, unless a prolonged break is required.
Oral TKI
## Indication: Targeted Tx

<table>
<thead>
<tr>
<th>Drug</th>
<th>Major indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>Advanced NSCLC</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>Advanced NSCLC</td>
</tr>
<tr>
<td>Everolimus</td>
<td>Advanced RCC, breast CA</td>
</tr>
<tr>
<td>Imatinib</td>
<td>CML, kit (+), GIST</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>HER-2(+) - breast cancer</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Advanced RCC, GIST</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>HCC, Advanced RCC</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>Advanced RCC, soft tissue sarcoma</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>CML</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>BRAF V600(+) - melanoma</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>Metastatic Colorectal cancer</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>ALK(+) - NSCLC</td>
</tr>
</tbody>
</table>
# Pharmacokinetic: Absorption & Solubility

<table>
<thead>
<tr>
<th></th>
<th>Absorption (bioavailability)</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erlotinib</strong></td>
<td>• 60% when taken on empty stomach</td>
<td>• pH dependent</td>
</tr>
<tr>
<td></td>
<td>• 100% when taken with food: ↑<strong>AUC 33%</strong> (potential S/E)</td>
<td>• Optimal solubility at pH &lt; 5</td>
</tr>
<tr>
<td><strong>Gefitinib</strong></td>
<td>• 60% (food doesn’t affect)</td>
<td>• Low solubility</td>
</tr>
<tr>
<td><strong>Lapatinib</strong></td>
<td>• Incomplete and variable</td>
<td>• Not mention about pH</td>
</tr>
<tr>
<td></td>
<td>• 1st pass metabolism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ↑AUC 3 fold: low fat (5% fat-500 cal)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ↑AUC 4 fold: high fat (10% fat-1000 cal)</td>
<td></td>
</tr>
<tr>
<td><strong>Sorafenib</strong></td>
<td>• 38-49%</td>
<td>• pH dependent</td>
</tr>
<tr>
<td></td>
<td>• ↓F 30% with high fat (50% fat-900 cal)</td>
<td>• ↓Solubility at pH↑</td>
</tr>
<tr>
<td><strong>Sunitinib</strong></td>
<td>• Food has no effect</td>
<td>Not mention about pH</td>
</tr>
</tbody>
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## Dosage and administration

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<th>Drug</th>
<th>Dose</th>
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<tr>
<td>Erlotinib (150 mg/tab)</td>
<td>150 mg OD</td>
<td>✔</td>
<td>✗</td>
</tr>
<tr>
<td>Geftinib (250 mg/tab)</td>
<td>250 mg OD</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>
| Lapatinib (250 mg/tab) | • With capecitabine 1250 mg OD D1-14 (21 d-cycle)  
• With letrozole 1500 mg OD (↑AUC 2-fold when divided dose) | ✔  | ✗ |
| Sorafenib (200 mg/tab)   | 400 mg bid                                                           | ✔  | ✗ |
| Sunitinib (12.5 mg/tab)  | • RCC and GIST 50 mg OD (schedule 4/2)  
• PNET 37.5 mg OD | ✔  | ✔  |
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<td>✗</td>
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<td><strong>Lapatinib</strong></td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Child-C:750 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sorafenib</strong></td>
<td>✗</td>
<td>200 mg OD</td>
<td></td>
</tr>
<tr>
<td>• Bilirubin &gt;1.5-≤ 3xULN: 200 mg b.i.d.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Bilirubin &gt;3-10 xULN (any AST): 200 mg q 3days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sunitinib</strong></td>
<td>✗</td>
<td>Initial at 25 mg OD and increased to 37.5 mg or 50 mg</td>
<td>✗</td>
</tr>
<tr>
<td>†use with extreme caution</td>
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TKI vs Acid-reducing agents

- Should the concomitant use of TKIs and acid reducing agents be avoided?????
TKI vs Acid-reducing agents

- **PPIs**
  - 20 mg Omeprazole:
    - Plasmatic t1/2 = 0.5-1 hr
    - Duration = 72 hr
    - 50-80% of basal gastric secretion is still inhibited 24 hr after dosing
    - ↑ Intragastric pH > 4 for a mean 11.8 hr (single dose) but increases with continuous dosing
    - ↓ AUC 46% and ↓ Cmax 61% of erlotinib

TKI vs Acid-reducing agents

- PPIs
  - Other PPIs, esomeprazole, lansoprazole, rabeprazole, have a comparable or longer duration

Separating admin. may not eliminate the problem

TKI vs Acid-reducing agents

- **H2RA**
  - 80 mg of ranitidine
    - ↑ gastric pH > 5 up to 12 hr
  - 300 mg of ranitidine
    - ↓AUC 33%, Cmax 54% of erlotinib
  - Erlotinib PO 2 hr before or 10 hr after 150 mg b.i.d of ranitidine
    - ↓AUC 15%, Cmax 17% of erlotinib
  - Cimetidine: enz. inhibitor

TKI vs Acid-reducing agents

- **Antacid**
  - Usual therapeutic doses: pH $> 4.5$
  - Suggest: Separating antacids from erlotinib by several hour
From evidence to clinical practice

- FDA required Drug-Drug interaction:
  > 20% change in Cmax or AUC to be included in monograph
- Only 3 P’cokinetic studies for PPI:
  - Unknown: clinical relevance of suboptimal absorption of erlotinib and whether it actually leads to failure of Tx
- Important: weigh benefit & risk because presently of unclear clinical significance
From evidence to clinical practice

Re-evaluate the indication for acid-reducing agents

- If pt is currently indicated for, symptom management & overall comfort: should be deemed a high priority
TKI vs Acid-reducing agents

- Impact of acid suppression on erlotinib’s pharmacokinetic is highest with omeprazole and expected to be similar significantly with PPI class.
- Antacid theoretically would have the least impact: short duration and lesser effect on gastric pH.
Pharmacokinetic: metabolism

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<tr>
<th>Drug</th>
<th>Hepatic</th>
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<th></th>
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<tbody>
<tr>
<td>Erlotinib</td>
<td>Oxidation: CYP 3A4 (major), CYP 1A2, 2C8 (minor)</td>
<td></td>
<td>Glucuronigation: -</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>Oxidation: CYP 3A4 (major), CYP 3A5, 2D6, 1A1 (minor)</td>
<td></td>
<td>Glucuronigation: -</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Oxidation: CYP3A4, 3A5 (major), CYP2C19, 2C8 (minor)</td>
<td></td>
<td>Glucuronigation: -</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Oxidation: CYP3A4</td>
<td></td>
<td>Glucuronination: UGT 1A9</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Oxidation: Substrate CYP3A4</td>
<td></td>
<td>Glucuronination: -</td>
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## Drug interaction

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<thead>
<tr>
<th>Drug</th>
<th>CYP3A4 inhibitor</th>
<th>CYP3A4 inducer</th>
</tr>
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<tbody>
<tr>
<td>Erlotinib</td>
<td>May require dose reduction in 50 mg decrements</td>
<td>↑50 mg increments at 2 wk intervals to a maximum of 450 mg</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>No data</td>
<td>500 mg OD</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>500 mg OD</td>
<td>1250mg → 4500 mg 1500mg → 5500 mg</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Consider 37.5 mg/d</td>
<td>Consider 87.5 mg/d</td>
</tr>
</tbody>
</table>
Drug interaction

CYP 3A4 inhibitor
- Azole
- Voriconazole
- Clarithromycin
- Erythromycin
- Diltiazem
- Verapamil
- Ritonavir
- Cimetidine
- Ciprofloxacin: CYP3A4, 1A2
- Grapefruit juice

CYP 3A4 inducer
- Rifampicin
- Phenytoin
- Phenobarbital
- Carbamazepine
- St. John wort
Case study

- A 53 years old woman
- Diagnosis: Lung cancer stage 4 with bone metastasis
- She has a history of standard chemotherapy with poor response
- Her doctors started Tarceva
- She meet you at OPD and ask about her foods and dietary supplements
- She usually take fishes, vegetables every meal and drink juice 4-6 glasses per day and tend to find the dietary supplement that she believes that these can fight with her diseases
<table>
<thead>
<tr>
<th>Vegetable</th>
<th>Molecular target</th>
<th>Drug Interactions in Humans and Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broccoli</td>
<td>Inhibits: CYP1A1, CYP2B1/2, CYP3A4, CYP2E1, hGSTA1/2, MRP-1, MRP-2, BCRP, UDP, Glucosyltransferases, Sulfoconjugases, Quinone reductases phenolsulfotransferases [26, 120, 121]</td>
<td>Not documented</td>
</tr>
<tr>
<td></td>
<td>Induces: UDPglucuronosyltransferases, (UGTs), sulfoxtransferases, (SULTs) and quinone reductases (QRs) [26]</td>
<td></td>
</tr>
<tr>
<td>Cauliflower</td>
<td>Inhibits: CYP1A1, CYP2B1/2, CYP3A4, CYP2E1, hGSTA1/2, MRP-1, MRP-2, BCRP, UDP, Glucosyltransferases, Sulfoconjugases, Quinone reductases phenolsulfotransferases [26, 120, 121]</td>
<td>Not documented</td>
</tr>
<tr>
<td></td>
<td>Induces: UDPglucuronosyltransferases, (UGTs), sulfoxtransferases, (SULTs) and quinone reductases (QRs) [26]</td>
<td></td>
</tr>
<tr>
<td>Watercress</td>
<td>Inhibits: CYP2E1, P-glycoprotein, MRP1, MRP2 and BCRP [26, 126]</td>
<td>In humans: Chlorzoxazone</td>
</tr>
<tr>
<td>Spinach</td>
<td>Possible inhibition of CYP1A2 [1132]</td>
<td>In vitro system: heterocyclic aromatic amines</td>
</tr>
<tr>
<td>Tomato</td>
<td>Inhibits: CYP1A1, CYP1B1, UGP, [138] Increases: UGT and CYP2E1, [139]</td>
<td>In vitro system: diethylnitrosamine, N-methyl-N-nitrosourea, and 1,2-dimethylhydrazine</td>
</tr>
<tr>
<td>Carrot</td>
<td>Induces: phenolsulfotransferases and ethoxycoumarin O-deethylase ECD [123, 143]</td>
<td>Not documented</td>
</tr>
<tr>
<td></td>
<td>Inhibits: CPY2E1 [122]</td>
<td></td>
</tr>
<tr>
<td>Avocado</td>
<td>Unknown</td>
<td>Humans: Warfarin</td>
</tr>
<tr>
<td>Red pepper</td>
<td>Inhibits CYP 1A2, 2A2, 3A1, 2C11, 2B1, 2B2 and 2C6 [154,155]</td>
<td>In vitro and in vivo</td>
</tr>
</tbody>
</table>

Fruit/Vegetable-Drug Interactions: Effects on Drug Metabolizing Enzymes and Drug Transporters
### Fruit/Vegetable-Drug Interactions: Effects on Drug Metabolizing Enzymes and Drug Transporters

<table>
<thead>
<tr>
<th>Fruit</th>
<th>Molecular Target</th>
<th>Drug Interactions in Humans and Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grapefruit</td>
<td>Inhibits CYP3A4, CYP1A2, MRP2, OATP-B and P-glycoprotein, [29, 45, 50, 53, 54, 65]</td>
<td>In humans: reports of more than 40 drug interactions: calcium channel antagonists [57], central nervous system modulators [58], HMG-CoA reductase [59], immunosuppressants [60], anti-virals [61], phosphodiesterases-5 inhibitor [62], antihistamines [63], antiarrhythmics [62], and antibiotics [64].</td>
</tr>
<tr>
<td>Tangerine</td>
<td>Stimulates CYP3A4 activity and inhibits P-glycoprotein [52]</td>
<td><em>In vitro</em> system: nifedipine [74], digoxina [52]</td>
</tr>
<tr>
<td>Grapes</td>
<td>Inhibits CYP3A4 and CYP2E1 [13]</td>
<td>In humans: cyclosporine [78],</td>
</tr>
<tr>
<td>Cranberry</td>
<td>Inhibits CYP3A and CYP2C9 [31, 81, 83]</td>
<td>In humans: Warfarin [81, 82]</td>
</tr>
<tr>
<td>Pomegranate</td>
<td>Inhibits CYP3A and phenol sulfotransferase activity [56,89]</td>
<td><em>In vitro</em> system: Diclofenac [83]</td>
</tr>
<tr>
<td>Mango</td>
<td>Inhibits CYP1A1, CYP1A2, CYP 3A1, CYP2C6, CYP2E1, P-glycoprotein (ABCB1) [97]</td>
<td><em>In vitro</em> system: midazolam, diclofenac, chlorzoxazone [95, 96]; Verapamil [97].</td>
</tr>
<tr>
<td>Guava</td>
<td>Inhibits P-glycoprotein [23]</td>
<td>Not documented</td>
</tr>
<tr>
<td>Black mulberry</td>
<td>Inhibits CYP3A and OATP-B [49]</td>
<td><em>In vitro</em> system: midazolam; glibenclamida [53]</td>
</tr>
<tr>
<td>Apple</td>
<td>Inhibits CYP1A1, OATP family (Oatp-1, Oatp-3 and NTCP) [63, 110]</td>
<td><em>In vitro</em> system: fexofenadine [63]</td>
</tr>
<tr>
<td>Papaya</td>
<td>Inhibits CYP3A4 [114]</td>
<td>No documented</td>
</tr>
</tbody>
</table>
Grapefruit Inhibits Metabolism of Many Drugs

- Flavonoids is responsible for drug interaction
- Inactivates metabolizing intestinal enzyme resulting in enhanced activity and possible toxicity
- Effect persists for 72 hours so it is not helpful to separate the drug and the grapefruit
Food-drug interaction
## Toxicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>Rash, diarrhea</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>Rash, diarrhea</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Diarrhea, Hand-foot syndrome, LVEF↓, Hepatitis</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Hand-foot syndrome, HTN, diarrhea, thyroid dysfunction, QT prolong, hepatitis</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Hand-foot syndrome, HTN, diarrhea, thyroid dysfunction, QT prolong, hepatotoxic</td>
</tr>
</tbody>
</table>
Special administration by NG tube

- Dissolve the tablet in 100 ml of water with resulting in suspension
- Rinse the container twice with 40 ml of water
Missing dose

- Gefitinib and Erlotinib:
  - If a dose is omitted over 12 hr, pt should wait for taking the next dose

- Sunitinib and Lapatinib:
  - Take as soon as you remember, but if it close to next dose, skip the miss dose and take your regular schedule

- Sorafenib:
  - skip the missed dose, and take your next dose at your regular time

- Should not take double dose on next day

- Vomiting???
Thank you very much