Oral Anticancer Therapy

Jitprapa Konmun

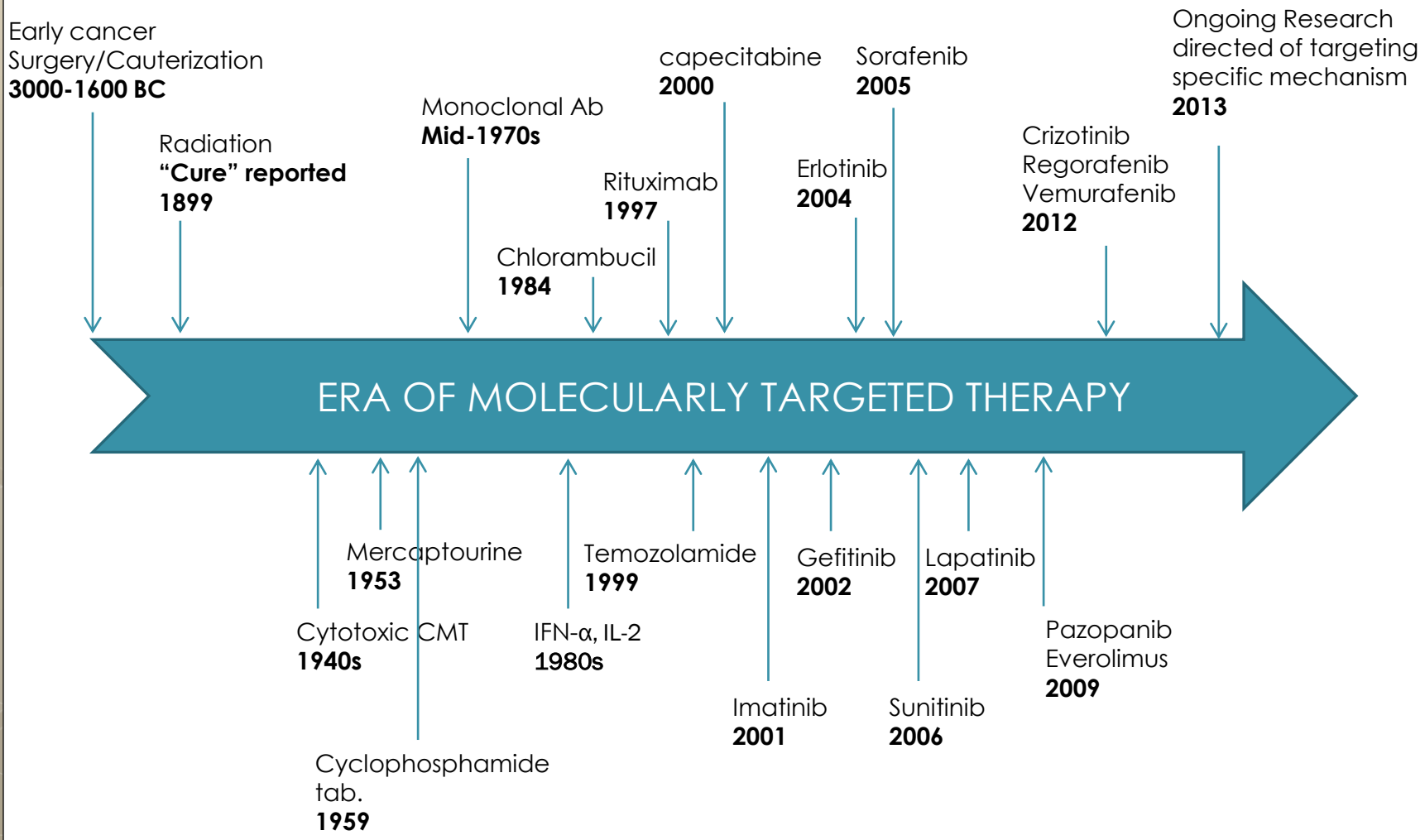
B. Pharm, Grad. Dip. in Pharmacotherapy, BCOP

Clinical Pharmacy, Ramathibodi Hospital

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



Introduction

- Oral chemotherapeutic drugs have been available for decades
  - Conventional Anticancer Oral Therapy (AOT)
    - Chlorambucil
    - Cyclophosphamide
    - Methotrexate
    - 6-mercapto-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

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

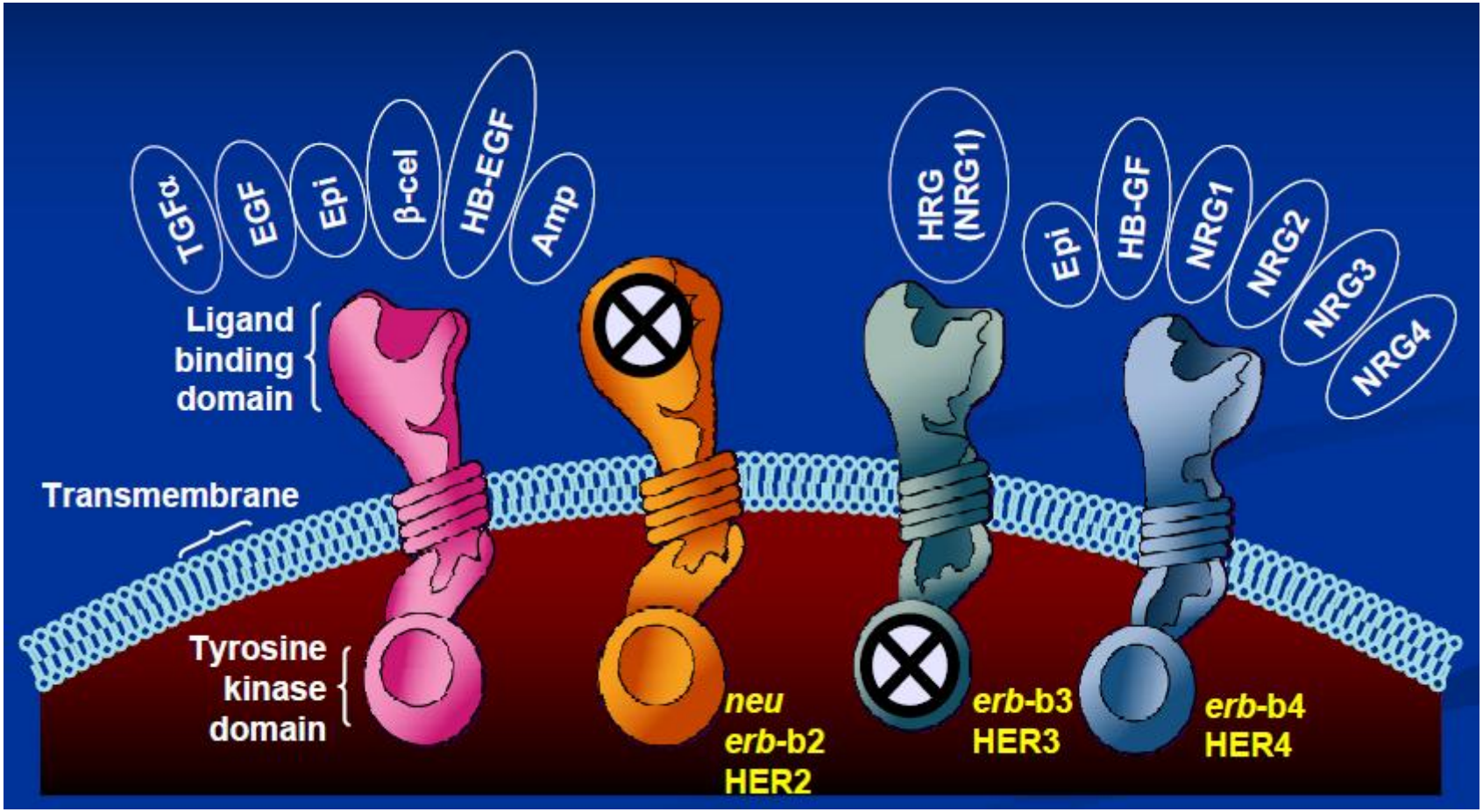
- Oral chemotherapy is changing model of therapy

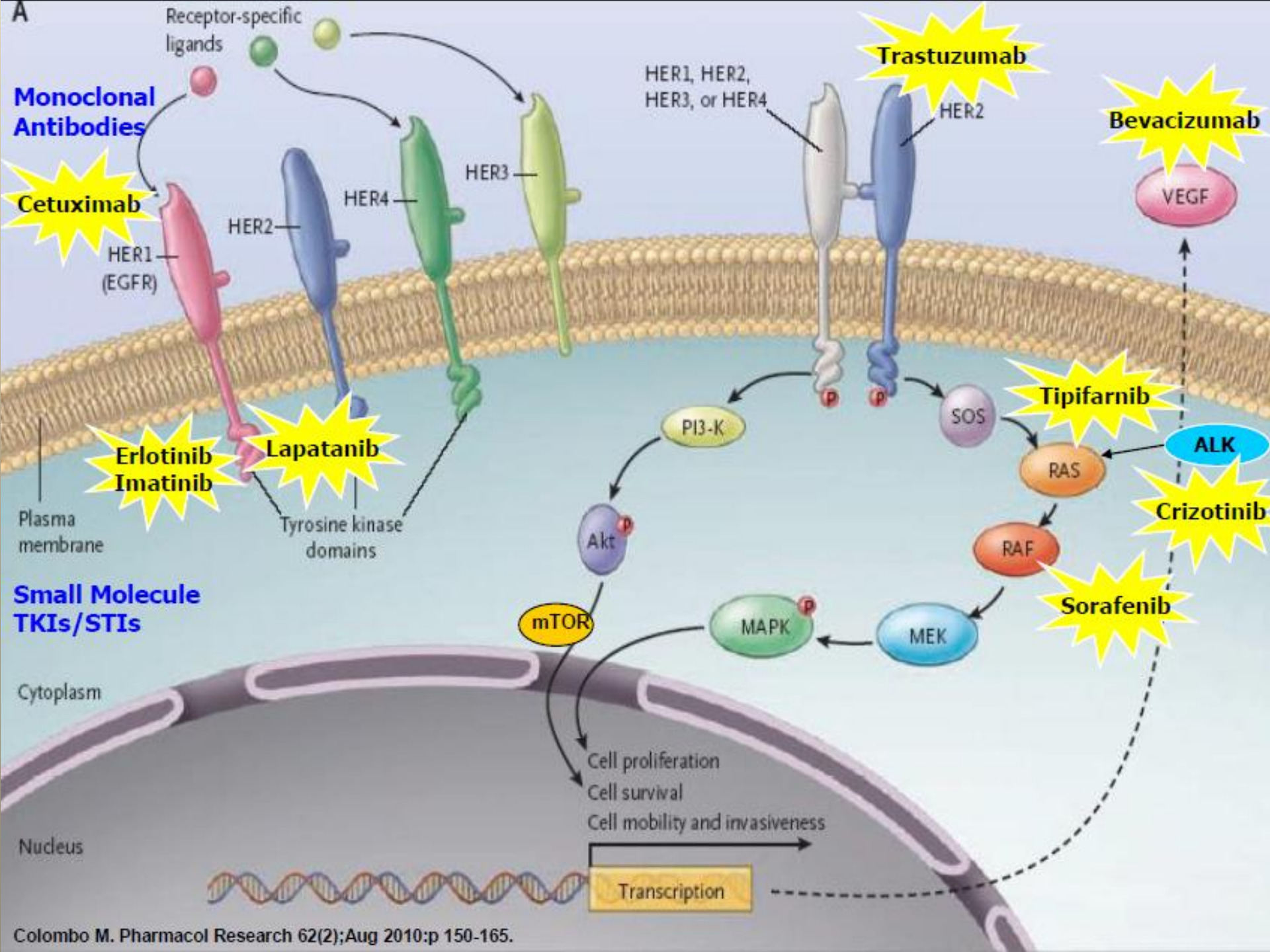
Targeted therapy

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





Colombo M. Pharmacol Research 62(2);Aug 2010:p 150-165.

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
  - xi = chimeric (both)
  - zu = humanized
  - u = human
  - e = hamster
  - i = primate
  - 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	Oral TKI
Capecitabine Cyclophosphamide Temozolamide	Gefitinib Erlotinib Lapatinib Sunitinib Sorafenib

Administration

Dose & Dose adjustment

Miss dose

ADR

Stability

Prevention and management ADR

Special administration

Drug –Drug & Drug - Food interaction

Oral Chemotherapy

Pharmacokinetic: Absorption&Solubility

	Absorption (bioavailability)
Cyclophosphamide	• >75% • Food don't have affect
Capecitabine	• Readily absorp • effect of food reduce the rate and extent absorption
Temozolamide	• Rapid and complete • To reduce nausea; take on empty stomach or bedtime

Dosage and administration

	Dose	ac	pc
Cyclophosphamide (25 mg/tab)	100 mg/m^2/day on D1-14 on 21 day cycle	✓	✓
Capecitabine (150, 500 mg)	Breast cancer: 1250 mg/m^2 bid on D1-14 on 21 day cycle Colon cancer: 1000 mg/m^2 bid on D1-14 on 21 day cycle	✗	✓ (within 30 min After meal)
Temozolamide (20,100 mg)	• 75 mg/m^2 OD CCRT followed by 150-200 mg/m^2 OD on D1-5 days q 28 days	✓ or hs	✗

Dose Adjustment

	Renal impairment	Hemodialysis patient¥	Hepatic impairment
Cyclophosphamide	✖ (yes for high dose)	• ↓25% • Give after HD	✖
Capecitabine	• Clcr 30-50 ml/mim:↓25% • Clcr < 30 ml/min: do not use	No data Should be avoid in HD pt	• Mild-moderate: ✖ • In severe hepatic : have not been studied
Temozolamide	✖	✖	✖

†use with extreme caution
¥For dialysis depend on which dialysis machine they use

Pharmacokinetic:metabolism

Drug	Metabolism
Cyclophosphamide	Hepatic to active metabolite Substrate of CYP2B6 (major)
Capecitabine	• Hepatic: extensively metabolized enzymatically • Inhibit CYP2C9 (strong)
Temozolamide	Spontaneously hydrolyzed at physiological pH to active species, MTIC (Dacarbazine)

Drug interaction

Cyclophosphamide	CYP 2B6 inh. (mod.): allopurinol CYP 2B6 inh. (strong): Denosumab, Etanercept
Capecitabine	CYP2C9 substrate: Phenytoin, carvedilol, leflunomide
Temozolamide	No

Special medication by NG-tube

Avoid crushing tablets

Use the injection to prepare an oral solution

should be undertaken in appropriate facilities

Special medication by NG-tube

Cyclophosphamide	• Extemporaneous liquid preparations for oral administration may be prepared by dissolving tablets in aromatic, Elixir. • Preparations should be stored under rerigeration 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

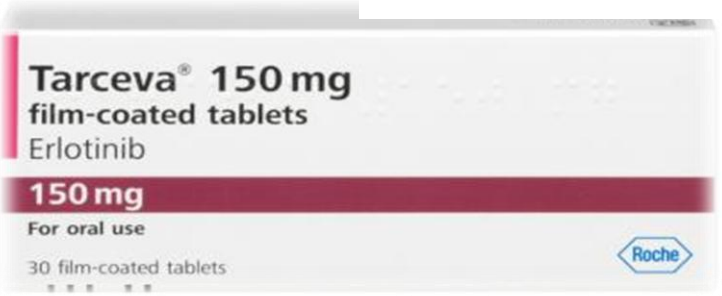
- Stop the enteral feed.
- Flush the enteral feeding tube with the recommended volume of water.
- Draw the medication solution into an appropriate size and type of syringe.
- Flush the medication dose down the feeding tube.
- Draw an equal volume of water into the syringe and also flush this via the 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


IRESSA 250 mg
filmdragerade tabletter/
kalvopäällysteiset tabletit/
õhukese polümeerikattega tabletid
gefitinib
Oral användning
Suun kautta
Suukaudseks manustamiseks
30
Iressa 250mg


Nexavar
Sorafenib (Tosilato)
Comprimidos recubiertos 200 mg
Vía Oral
Caja con 60 comprimidos


SUTENT
SUTENT
SUTENT


Tarceva® 150 mg
film-coated tablets
Erlotinib
150 mg
For oral use
30 film-coated tablets
Roche

Indication: Targeted Tx

Drug	Major indication
Erlotinib	Advanced NSCLC
Gefitinib	Advanced NSCLC
Everolimus	Advanced RCC, breast CA
Imatinib	CML, kit (+),GIST
Lapatinib	HER-2(+)-breast cancer
Sunitinib	Advanced RCC, GIST
Sorafenib	HCC, Advanced RCC
Pazopanib	Advanced RCC, soft tissue sarcoma
Dasatinib	CML
Vemurafenib	BRAF V600(+) melanoma
Regorafenib	Metastatic Colorectal cancer
Crizotinib	ALK(+) NSCLC

Pharmacokinetic: Absorption&Solubility

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

Dosage and administration

	Dose	ac	pc
Erlotinib (150 mg/tab)	150 mg OD	✓	✗
Geftinib (250 mg/tab)	250 mg OD	✓	✓
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	✓	✓

Dose Adjustment

	Renal impairment	Hemodialysis patient	Hepatic impairment
Erlotinib	×	×	×
Gefitinib	×	×	×
Lapatinib	×	×	✓ Child-C:750 mg
Sorafenib	×	200 mg OD	• Bilirubin >1.5-≤ 3xULN: 200 mg b.i.d. • Bilirubin >3-10 xULN (any AST): 200 mg q 3days
Sunitinib †use with extreme caution	×	Initial at 25 mg OD and increased to 37.5 mg or 50 mg	×

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**

Doung S, Leung M. J Oncol Pharm Practice 2010;17(4):448-452.
Miner P, et al. Am J Gastro 2003;98:2616-2620.

TKI vs Acid-reducing agents

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

Separating admin. may not eliminate the problem

Miner P, et al. Am J Gastro 2003;98:2616-2620.

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

Doung S, Leung M. J Oncol Pharm Practice 2010;17(4):448-452.

TKI vs Acid-reducing agents

- **Antacid**
  - Usual therapeutic doses: pH $\not>$ 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 p'cokinetic is highest with omeprazole and expected to be similar sig. with PPI class
- Antacid theoretically would have the least impact : short duration and lesser effect on gastric pH

Pharmacokinetic:metabolism

	Hepatic	
	Oxidation	Glucuronigation
Erlotinib	CYP 3A4 (major), CYP 1A2, 2C8 (minor)	-
Gefitinib	CYP 3A4 (major), CYP 3A5, 2D6, 1A1 (minor)	-
Lapatinib	CYP3A4, 3A5 (major) CYP2C19,2C8 (minor)	-
Sorafenib	CYP3A4	UGT 1A9
Sunitinib	Substrate CYP3A4	-

Drug interaction

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

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 women
- 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, vegatables every meals 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

Vegetable	Molecular target	Drug Interactions in Humans and Others.
Broccoli	Inhibits: CYP1A1, CYP2B1/2, CYP3A 4, CYP2E1, hGSTA1/2, MRP-1, MRP-2, BCRP, UDP, Glucorosytransferases, Sulfotransferases, Quinone reductases phenolsulfotransferases [26, 120,121] Induces: UDPglucuronosyltransferases, (UGTs), sulfotransferases, (SULTs) and quinone reductases (QRs) [26]	Not documented
Cauliflower	Inhibits: CYP1A1, CYP2B1/2, CYP3A 4, CYP2E1, hGSTA1/2, MRP-1, MRP-2, BCRP, UDP, Glucorosytransferases, Sulfotransferases, Quinone reductases phenolsulfotransferases [26,120, 121] Induces: UDPglucuronosyltransferases, (UGTs), sulfotransferases, (SULTs) and quinone reductases (QRs) [26]	Not documented
Watercress	Inhibits: CYP2E1, P-glycoprotein, MRP1, MRP2 and BCRP [26, 126]	In humans: Chlorzoxazone
Spinach	Possible inhibition of CYP1A2 [1132]	*In vitro* system: heterocyclic aromatic amines
Tomato	Inhibits: CYP1A1, CYP1B1, UGP, [138] Increases: UGT and CYP2E1, [139]	In vitro system: diethylnitrosamine, N-methyl-N-nitrosourea, and 1,2-dimethylhydrazine
Carrot	Induces: phenolsulfotransferases and ethoxycoumarin O-deethylase ECD [123, 143] Inhibits: CPY2E1 [122]	Not documented
Avocado	Unknown	Humans: Warfarin
Red pepper	Inhibits CYP 1A2, 2A2, 3A1, 2C11, 2B1, 2B2 and 2C6 [154,155]	*In vitro* and *in vivo*

Fruit	Molecular Target	Drug Interactions in Humans and Others
Grapefruit	Inhibits CYP3A4, CYP1A2, MRP2, OATP-B and P-glycoprotein, [29, 45, 50, 53, 54, 65]	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], antiarrythmics [62], and antibiotics [64].
Sevilla orange	Inhibits CYP3A4, P-glycoprotein, OATP-A, OATP-B [11, 29, 5469, 117]	*In vitro* system: vinblastine [55], fexofenadine [29], glibenclamida [53] In humans: atenolol, ciprofloxacine, ciclosporine, celiprolol, levofloxacin and pravastatin [54, 72]
Tangerine	Stimulates CYP3A4 activity and inhibits P-glycoprotein [52]	*In vitro* system: nifedipine [74], digoxina [52]
Grapes	Inhibits CYP3A4 and CYP2E1 [13]	In humans: cyclosporine [78],
Cranberry	Inhibits CYP3A and CYP2C9 [31, 81, 83]	In humans: Warfarin [81, 82] *In vitro* system: Diclofenac [83]
Pomegranate	Inhibits CYP3A and phenol sulfotransferase activity [56,89]	Animals: carbamacepine [56]
Mango	Inhibits CYP1A1, CYP1A2, CYP 3A1, CYP2C6, CYP2E1, P-glycoprotein (ABCB1) [97]	*In vitro* system: midazolam, diclofenac, chlorzoxazone [95, 96]; Verapamil [97].
Guava	Inhibits P- glycoprotein [23]	Not documented
Black raspberry	Inhibits CYP3A [49]	*In vitro* system: midazolam
Black mulberry	Inhibits CYP3A and OATP-B [49]	*In vitro* system: midazolam; glibenclamida [53]
Apple	Inhibits CYP1A1, OATP family (Oatp-1, Oatp-3 and NTCP) [63, 110]	*In vitro* system: fexofenadine [63]
Papaya	Inhibits CYP3A4 [114]	No documented

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

Grapefruit Inhibits Metabolism of Many Drugs

- Flavonids 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

Drug	Toxicity
Erlotinib	Rash, diarrhea
Gefitinib	Rash, diarrhea
Lapatinib	Diarrhea, Hand-foot syndrome, LVEF↓, Hepatitis
Sorafenib	Hand-foot syndrome, HTN, diarrhea, thyroid dysfunction, QT prolong,hepatitis
Sunitinib	Hand-foot syndrome, HTN, diarrhea, thyroid dysfunction, QT prolong, hepatotoxic

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